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Long-Term Outcomes of Prolonged Exposure and Naltrexone for Patients with Comorbid Posttraumatic Stress Disorder and Alcohol Dependence

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Long-Term Outcomes of Prolonged Exposure and Naltrexone for Patients with Comorbid Posttraumatic Stress Disorder and Alcohol Dependence

A dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy at Virginia Commonwealth University.

by

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Abstract

LONG-TERM OUTCOMES OF PROLONGED EXPOSURE AND NALTREXONE FOR PATIENTS WITH COMORBID POSTTRAUMATIC STRESS DISORDER AND ALCOHOL DEPENDENCE

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A dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy at Virginia Commonwealth University.

Virginia Commonwealth University, 2014.

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A growing body of research is examining effective treatment(s) for individuals with comorbid posttraumatic stress disorder (PTSD) and alcohol dependence (AD). However, treatments for this comorbid population have been inadequately studied in the longer term. This study represents a long-term follow-up assessment of a randomized controlled trial that compared combined therapy (prolonged exposure + naltrexone) with monotherapies (prolonged exposure or naltrexone) for patients with PTSD and AD (see Foa, Yusko, McLean et al., 2013). Attempts were made to contact 120 participants 5-10 years after the original trial to assess the maintenance of treatment gains. Nineteen individuals were located and agreed to participate. A series of mixed ANCOVAs were conducted with PTSD symptom severity and percentage of days drinking and heavy drinking as the dependent variables. Findings revealed that reductions in PTSD symptoms and drinking behaviors generally were maintained 5-10 years after treatment. There was some relapse in heavy drinking days, and combination treatment was most effective for long-term PTSD outcomes. Challenges of conducting follow-up research with this population, implications and limitations of the present findings, and directions for future research are discussed.
Long-Term Outcomes of Prolonged Exposure and Naltrexone for Patients with Comorbid Posttraumatic Stress Disorder and Alcohol Dependence

Posttraumatic stress disorder (PTSD) is characterized by the development of symptoms following exposure to an extreme traumatic stressor (DSM-IV-TR). Symptoms are grouped into three clusters: a) re-experiencing of the event (e.g., recurrent and intrusive thoughts, distressing dreams), b) avoidance and emotional numbing (e.g., avoidance of reminders of the traumatic event, restricted range of affect), and c) hyperarousal (e.g., sleep difficulties, exaggerated startle response) (American Psychiatric Association, 2000). PTSD occurs in approximately 8% of the United States population (Breslau, Davis, Andreski, & Peterson, 1991; Davidson & Fairbank, 1993; Kessler, Sonnega, Bromet et al., 1995) and is marked by a chronic course, such that symptoms typically persist 10 years after onset (Kessler et al., 1995; Owashi & Perkonigg, 2007). PTSD is characterized by high rates of suicidal ideation, attempts, and completions (Tarrier & Gregg, 2004). Additionally, PTSD is associated with more health problems and higher utilization of medical services than the general population (Deykin, Keane, Kaloupek et al., 2001). Clearly, PTSD is a serious disorder that affects many individuals who have been exposed to a traumatic event.

It is estimated that 80% of individuals with PTSD suffer from another Axis I psychiatric disorder (Foa, Keane, & Friedman, 2000). In men, the most common co-occurring disorder is alcohol dependence (51.9%) and in women it is the fourth most common diagnosis (27.9%; Fear, Jones, Murphy et al., 2010; Kessler et al., 1995). Alcohol dependence (AD) is a progressive chronic disorder that poses a heavy burden on patients, their families, and society (American Psychiatric Association, 1994). AD affects approximately 10% of Americans at some time in their lives (Caetano & Tam, 1995; Grant, 1997; Grant, Peterson, Dawson et al., 1994; Regier,
Farmer, Rae et al., 1990). In addition to the 100,000 United States citizens who die each year because of alcohol-related causes, including traffic collisions and cirrhosis of the liver (McGinnis & Foege, 1993), AD costs the nation an estimated $166 billion annually in direct and indirect health and social costs (National Institute on Drug Abuse, National Institute on Alcohol Abuse and Alcoholism, 1998). The prevalence rate and consequences highlight the public health significance of AD.

Specifically, 28% of women and 52% of men with PTSD show comorbid alcohol abuse and/or dependence (Kessler et al., 1995). The base rates for the comorbid conditions are significantly higher than the population base rates for either disorder individually (Breslau, Davis, & Schultz, 2003). Among patients with PTSD, those with comorbid AD have more severe PTSD symptoms, more dissociative symptoms, and more borderline personality characteristics than those with only PTSD (Behar, 1987; Ouimette, Wolfe, & Crestman, 1996; Saladin, Brady, Dansky, & Kilpatrick, 1995). Among alcohol abusers, trauma history is associated with more severe substance dependence (e.g., Schumacher, Coffey, & Stasiwicz, 2006), greater levels of general psychopathology (Harvey, Rawson, & Obert, 1994), and higher rates of antisocial personality, depression, generalized anxiety, and suicidality (Tarrier & Gregg, 2004; Windle, Windle, Schedit, & Miller, 1995). In general, the functional deficits among PTSD/AD patients are more severe than comparable samples of PTSD and AD alone.

Despite the prevalence of these comorbid diagnoses and consistent associations between comorbid PTSD and AD and poor outcomes, relatively little is known about effective treatment for this comorbid population. Cognitive-behavioral therapy, and in particular prolonged exposure (PE) therapy, has significant empirical support in treating PTSD. In fact, the effectiveness of exposure therapy for PTSD has been demonstrated more than any other treatment (Foa &
Rothbaum, 1998; Rothbaum, Meadows, Resick, & Foy, 2000). There are also several medications, particularly naltrexone, with a verified efficacy for the reduction of alcohol intake and relapse risk by AD individuals (Anton, Moak, Waid et al., 1999; O’Malley, Jaffe, Chang et al., 1992; Volpicelli, Alterman, Hayashida, & O’Brien, 1992; Volpicelli, Rhines, Rhines et al., 1997; Volpicelli, Volpicelli, & O’Brien, 1995). Therefore, there are effective treatments for individuals with PTSD and individuals with AD, but there is little research on treatment for individuals with both disorders.

The importance of treating both conditions simultaneously is highlighted by the cycle that exists among patients with comorbid PTSD and AD. Alcohol, particularly among individuals with AD, may function to regulate the negative emotions associated with PTSD symptoms (e.g., Chilcoat & Breslau, 1998; Stewart, Pihl, Conrod, & Dongier, 1998). Interoceptive cues, such as PTSD-related fear and anxiety, become conditioned stimuli that may precipitate increased cravings and drinking in individuals with AD (e.g., Cooney, Litt, Morse et al., 1997; Greeley, Swift, & Heather, 1992; Litt, Cooney, Kadden, & Gaupp, 1990). Therefore, PTSD symptoms are implicated in the development and maintenance of alcohol use and alcohol use disorders (Coffey, Stasiewicz, Hughes, & Brimo, 2006). Conversely, alcohol leads to emotional numbing and cognitive avoidance, thereby serving to maintain two primary PTSD symptoms. Fear activation is crucial to successful outcomes in the treatment of PTSD and cannot be maximized with co-occurring drinking (Zaslav, 1994; Zweben, Clark, & Smith, 1994). Given the interaction between the two conditions, failure to attend to one can compromise the success of treatment for the other.

Clearly, it is important to identify an optimal treatment approach for patients with comorbid PTSD and AD (Foa & Williams, 2010). This is a population in dire need of effective
interventions due to their risk and associated impairments, but has been under-researched because of concerns about interference, premature termination, and relapse. Unfortunately, PTSD patients with comorbid AD have typically been excluded from PTSD studies due to concerns about the effect of exposure to trauma-related situations on drinking. That is, it was assumed that the stress of exposure therapy would increase alcohol use in patients with AD and that these patients would be at high risk for premature termination (Abueg & Fairbank; 1992; Schnitt & Nocks, 1984; Solomon, Gerrity, & Muff, 1992). There were also concerns that in treating AD in patients with PTSD, relapse would be high, given the use of alcohol as a means of coping with PTSD (Riggs, Rukstalis, Volpicelli et al., 2003). Such concerns have resulted in some of the most dysfunctional and distressed PTSD patients being excluded from PTSD treatment studies.

Recently, researchers have begun to examine effective treatment(s) for this population, and have found that treating both disorders concurrently is most effective in minimizing the negative effects of one disorder on the other (Back, Brady, Sonne et al., 2006; Coffey et al., 2006; Petrakis, Poling, Levinson et al., 2006). They have emphasized the need for concurrent treatment of AD problems and PTSD symptoms (Abueg & Fairbank, 1992; Najavits, Weiss, & Liese, 1996; Stine & Kosten, 1995). Patients perceive their AD and PTSD to be functionally related and report preferring concurrent treatment to sequential treatment of their comorbidities (Brown, Stout, & Gannon-Rowley, 1998). The research that has been conducted has suggested that combined treatment is most effective in treating comorbid PTSD and AD.

Although concurrent treatment is effective in treating comorbid PTSD and AD in the short-term, it has been inadequately studied in the longer term. It is important to examine the long-term outcomes of these established treatments, given the risk for relapse, particularly with
AD, and the interaction between alcohol use and PTSD. That is, relapse after discontinuation of naltrexone appears high (O’Malley, Jaffe, Chang et al., 1996). Furthermore, patients with comorbid PTSD are likely to be less compliant with treatment and may lack motivation because abstinence may exacerbate their PTSD symptoms. Therefore, it is important to understand treatments that will improve long-term prospects for patients with comorbid PTSD and AD.

This study represents a long-term follow-up assessment of a randomized controlled trial that compared combined therapy with monotherapies for patients with PTSD and AD (Foa, Yusko, McLean et al., 2013). In order to provide the background for this study, the literature on treatment for AD and PTSD is first reviewed. The review focuses on cognitive-behavioral therapy for PTSD given the demonstrated efficacy of several CBT programs. Studies comparing one form of CBT with another have favored exposure therapy, and therefore prolonged exposure was chosen for the randomized controlled trial (RCT) that the present study follows-up. For AD, naltrexone in conjunction with psychosocial support or CBT produces superior outcome than placebo with support or CBT; therefore naltrexone was chosen as the treatment for AD. The review then focuses on the existing literature of long-term follow-up studies for each type of treatment, highlighting methodological limitations of these follow-up studies. Treatment for comorbid PTSD and general substance use disorders is reviewed, followed by a review of literature focusing specifically on treatment for PTSD and AD. Finally, the randomized controlled trial that examined treatment for comorbid PTSD and AD is presented followed by an overview of the present study.
Literature Review

Naltrexone Efficacy Studies for Alcohol Dependence

Naltrexone is an opioid receptor antagonist that is used as a relapse prevention agent as an adjunct to psychosocial therapies for treating alcohol dependence (AD; Streeton & Whalen, 2001). In naltrexone trials, no mortality was reported and the most common adverse effects were nausea and dizziness. The naltrexone safety and tolerability study reported a 15% discontinuance rate for naltrexone subjects because of adverse events (Croop, Faulkner, & Labriola, 1997). Naltrexone has established efficacy in treating AD (Garbutt, West, Carey, Lohr, & Crews, 1999) and is the only FDA-approved medication whose efficacy for AD is supported by a large multi-center clinical trial conducted in the United States (Anton, O’Malley, Ciraulo et al., 2006). In general, when the drug is taken daily, it reduces the number of occasions a person is likely to drink and the amount of alcohol consumed in one occasion (Streeton & Whalen, 2001). A meta-analysis evaluating the aggregate efficacy and potential toxicity of naltrexone compared to placebo as an adjunct treatment for AD (13 articles, 7 separate trials) found that naltrexone is consistently more effective than placebo (Streeton & Whelan, 2001). In sum, 804 subjects across the different studies exhibited improved outcomes with respect to relapse rates, abstinence rates, and alcohol consumption measures compared to placebo over a short-term treatment period of 12 weeks.

Naltrexone efficacy studies have primarily consisted of a 12-week double-blind, placebo-controlled trial. Researchers consistently found that patients who took naltrexone had significantly fewer alcohol cravings and days in which any alcohol was consumed (Balldin, Berglund, Borg et al., 2003; O’Malley et al., 1992; Volpicelli et al., 1992), higher rates of abstinence and lower rates of relapse (Anton et al., 1999; Guardia, Caso, Arias et al., 2002;
O’Malley et al., 1992), fewer alcohol, drug, and employment problems (O’Malley et al., 1992), longer duration to first relapse, and more time between relapses (Anton et al., 1999). The authors concluded that naltrexone is a safe and effective adjunct to treatment in alcohol-dependent patients.

An important component of successful pharmacological treatment for AD is psychotherapy (Anton et al., 1999; Hunt & Azrin, 1973; Kiefner et al., 2003). Several studies demonstrated the efficacy of cognitive-behavioral methods with naltrexone in the treatment of AD. In these studies, CBT consisted of instructions in self-monitoring and functional analyses of drinking and urges, generating activities in lieu of drinking, and encouragement to develop strategies to prevent relapse (Balldin et al., 2003; O’Malley et al., 1992). Studies found an interaction between the medication and psychotherapy, such that naltrexone plus CBT is most effective in duration to first drinking episode and relapse into heavy drinking (Anton et al., 1999; Balldin et al., 2003; Guardia et al., 2002; O’Malley et al., 1992). Therefore, researchers have concluded that naltrexone can be particularly effective when used in conjunction with weekly outpatient cognitive-behavioral therapy.

**Long-Term Follow-Up Naltrexone Studies**

Although naltrexone has established short-term efficacy for the treatment of alcohol dependence, most studies are limited in the outcome being assessed only after three months. Therefore, the authors of the aforementioned studies preclude conclusions about long-term effectiveness of naltrexone (e.g., O’Malley et al., 1992). The hypothesis for naltrexone’s mechanism of action is that it aids recently abstinent individuals with AD by reducing cravings (Anton et al., 1999; Volpicelli et al., 1992) or by inhibiting reinforcement after slip drinking (O’Malley et al., 1996; Volpicelli et al., 1995). A concern is whether the positive effects
observed when naltrexone is added to psychosocial treatment during early recovery periods are maintained once the medication is discontinued. That is, it is unclear whether individuals with AD will maintain their gains and continue in a non-relapsed state after 12 weeks of medication or whether longer treatment is needed. Furthermore, animal studies have suggested that naltrexone-induced opiate receptor blockade may lead to immediate increases in alcohol consumption once the medication is stopped (Sinclair, 1990). Therefore, it is important to examine how alcohol consumption and cravings may change in the weeks following discontinuation. According to Streeton and Whelan (2001), one of the primary limitations of the existing studies on the efficacy of naltrexone is the brief duration of the study and outcome data. Only a few studies have been extended to include follow-ups that reevaluated original outcomes after discontinuation of naltrexone. These studies are reviewed below.

Several studies found that naltrexone continues to promote abstinence long-term. Landabaso and colleagues (1999) conducted a two-year post-baseline follow-up study evaluating the effectiveness of low-dose naltrexone (25 mg) among 30 alcoholics. Patients were randomly assigned to one of two groups: a) one year of aversion treatment plus a low dose of naltrexone during the first six months (experimental group); or b) aversion treatment only for one year (control group). Abstinence and relapse rates were analyzed at 12, 18, and 24 months. The authors found that the probability of remaining abstinent at all timepoints was greater in the naltrexone group than the control group. These findings suggest that the combined treatment of aversion and naltrexone would be effective in patients with multiple relapses who are refractory in treatment.

Rubio and colleagues (2002) conducted a randomized controlled trial to establish the duration of the effect after discontinuing naltrexone. The study consisted of 60 patients with AD
participating in a three-month treatment period of controlled drinking + naltrexone or controlled drinking alone, and a 12-month follow-up period. At one-year follow-up, the number of drinking days and the number of drinks were lower in the naltrexone group than in the standard treatment group. Importantly, naltrexone-treated patients were significantly less likely to drink heavily than patients who had received placebo for up to four months following naltrexone cessation. These findings suggest that naltrexone has long-term efficacy, even after discontinuation, and particularly when combined with a therapeutic drinking program.

One study found that, although naltrexone remained superior to placebo at follow-up, the benefit diminished over time. O’Malley and colleagues (1996) examined clinical outcomes over the six-month period following treatment termination for the patients who participated in the 12-week controlled trial of naltrexone and psychotherapy in the treatment of alcohol dependence. Results revealed that some, but not all, of the benefits resulting from short-term treatment with naltrexone persist after discontinuation. Although naltrexone resulted in higher abstinence rates during treatment, this effect was no longer apparent by the second month of follow-up. Conversely, the percentage of patients who avoided relapse over the entire follow-up was higher for the naltrexone than placebo group. Additionally, patients who had received naltrexone were significantly less likely to meet criteria for a diagnosis of alcohol abuse or dependence over the course of follow-up. Finally, patients who completely abstained during treatment had significantly better outcomes at six months, irrespective of medication condition. In general, naltrexone patients continued to experience lower relapse rates and fewer alcohol-related consequences following discontinuation, although this advantage diminished over the follow-up period.
Contrary results to the long-term superiority of naltrexone were found in a study evaluating the outcome in patients with alcohol dependence during the 14 weeks after a 12-week treatment with naltrexone or placebo in conjunction with CBT (Anton, Moak, Latham et al., 2001). Of the 131 patients evaluated during the acute treatment phase, 124 (95%) had post-treatment data available. Once the medication was discontinued, there was a gradual increase in relapse rates, heavy drinking days, and drinks per drinking day, and fewer days of abstinence were reported. By the end of the 14-week follow-up period, the effectiveness of naltrexone was no longer statistically significant. These data suggest that continued treatment with naltrexone or psychosocial intervention for longer than three months is indicated.

One study examined the long-term efficacy of allocation to one year of naltrexone (Rubio, Jimenez-Arriero, Ponce, & Palomo, 2001). At the end of one year, 41% receiving naltrexone had not relapsed. Naltrexone was associated with reduced relapse, more days of accumulated abstinence, reduction in total drinks consumed at any one time, and reduced craving. The results are consistent with previous naltrexone studies and the study is four times longer than the shorter-term studies, suggesting that long-term treatment of patients with naltrexone is beneficial. It is possible that naltrexone increases the period elapsed before the patient takes the first drink, which enables the learning of strategies taught in therapy and increases feelings of self-efficacy.

Extant studies on the long-term efficacy of naltrexone in the treatment of alcohol dependence have mixed findings. Some studies have found that the benefits of naltrexone are maintained over time. Others have found that the advantage of naltrexone in reducing relapse rates and alcohol-related consequences following discontinuation diminishes over the follow-up period, suggesting that continued treatment with naltrexone or psychosocial intervention for
longer than three months is indicated. Given that AD is a condition typically marked by chronic relapse, it is particularly important to determine the optimal duration of treatment with naltrexone. Streeton and Whelan (2001) strongly recommend additional follow-up studies with comparison groups and longer-term outcome results to evaluate the efficacy of naltrexone.

**Naltrexone Uses in Comorbid Populations**

Although naltrexone is approved and efficacious for alcohol dependence alone, the efficacy of naltrexone in comorbid populations is unclear. Dually-diagnosed patients tend to be non-compliant with treatment (Drake, Bartels Teague, Noordsy, & Clark, 1993), be at higher risk for suicide (Tondo, Baldessarini, Hennen et al., 1999), and have poorer treatment outcomes (Ho, Tsuang, Liberman et al., 1999). Diagnosis and treatment are complicated by the complex interactions between AD and comorbid diagnoses (Maxwell & Shinderman, 2000). Given the need for effective treatments for patients with comorbidity, evaluating the efficacy of naltrexone for patients with AD and a comorbid diagnosis is important. A small but growing literature has suggested that naltrexone may be safely used in patients with comorbid psychiatric disorders (Maxwell & Shinderman, 2000; Mueser, Noordsy, Fox, & Wolfe, 2003; Salloum, Cornelius, Thase et al., 1998).

One case review evaluated the efficacy of naltrexone in patients with alcohol dependence and a comorbid mental illness. Maxwell and Shinderman (2000) examined 72 patients being treated with naltrexone for alcohol use disorders who have at least one comorbid Axis I disorder. Psychiatric diagnoses included major depression (50.7%), schizophrenia (23.3%), bipolar disorder (15.1%), schizoaffective disorder (5.5%), and gender identity disorder (4.1%). They found that naltrexone resulted in a good clinical response and was well tolerated among this population. Patients reported a gradual decline in daily drinking upon initiation of naltrexone.
Findings from this study suggested that naltrexone has positive results in the treatment of alcohol use-disordered patients with concomitant major psychiatric disorders. Controlled clinical studies with a longer follow-up to more accurately describe the use of naltrexone in mentally ill patients with alcohol use disorders are an important next step.

**Naltrexone uses in PTSD samples.** A small literature exists evaluating the effect of naltrexone on PTSD symptoms because of its mechanism of action on the opioid receptor. One early report showed improvements in PTSD symptoms with naltrexone (Bills & Kreisler, 1993) and a more recent but short-term study with naltrexone (Lubin, Weizman, Shmushkevitz et al., 2002) reported significant but not clinically meaningful reduction of only the re-experiencing and hyperarousal symptoms in PTSD patients. One case report suggested that naltrexone may exacerbate psychiatric symptoms associated with PTSD, particularly rage and explosive behavior (Ibarra, Bruehl, McCubbin et al., 1994).

Petrakis and colleagues (2006) evaluated the relationship between PTSD and alcohol use in terms of treatment response to naltrexone, the effect of naltrexone on PTSD symptoms, and the relationship between PTSD and side effects/adverse events associated with naltrexone. Following a 12-week randomized trial, they found that patients with PTSD had better alcohol outcomes on naltrexone than they did on placebo, and psychiatric symptoms of PTSD improved over time and were not adversely affected by naltrexone. Additionally, patients in this study achieved a high rate of abstinence, and there were no re-emergence effects of psychiatric symptoms. The best outcomes were of the individuals who were abstinent throughout the trial. This finding highlights the importance of treating comorbid alcohol dependence in patients with PTSD.
The little research that has been conducted has suggested that naltrexone is an effective and safe pharmacotherapeutic agent for this group of patients and should be considered in the clinical management of patients with PTSD and alcohol dependence. Naltrexone may help uncomplicate the interactions between AD and comorbid diagnoses and may even secondarily address PTSD symptoms.

**Prolonged Exposure Efficacy Studies for PTSD**

Cognitive-behavioral interventions are the most studied psychosocial treatments for PTSD. In particular, exposure therapy was selected in a consensus statement compiled by the International Consensus Group on Depression and Anxiety as the most appropriate form of psychotherapy to manage PTSD. Exposure treatments involve techniques designed to help patients confront feared situations, objects, memories, or images.

Prolonged exposure (PE) for PTSD has received the most empirical evidence for its efficacy and will be briefly reviewed given the multitude of CBT, and even PE, studies for PTSD. It has shown to be highly effective for patients with a wide variety of traumatic experiences. In a series of randomized controlled trials, PE demonstrated large treatment effects compared to waitlist control groups, and similar effects compared to other active treatments, such as stress inoculation training, cognitive processing therapy, and eye movement desensitization (Foa, Hembree, Cahill et al., 2005; Marks, Lovell, Noshirvani, Livanou, & Thrasher, 1998; Paunovic & Ost, 2001; Resick, Nishith, Weaver, Astin, & Feuer, 2002; Rothbaum, Astin, & Marsteller, 2005). A recent meta-analysis found a large effect size for PE compared to waitlist or control active treatments at post-treatment and follow-up (Powers, Halpern, Perenschak, Gillihan, & Foa, 2010). PE is well tolerated by patients (Hembree, Foa,
Dorfan et al., 2003) and does not cause long-term exacerbation of symptoms (Foa, Zoellner, Feeny, Hembree, & Alvarez-Conrad, 2002).

**Long-Term Follow-Up CBT Studies for PTSD**

A question remains about whether PTSD symptom reductions resulting from CBT are long lasting. Although results point to the efficacy of CBT in treating patients with PTSD, longer-term follow-up of patients is a vital next step (Weisz & Hawley, 1998). It is important to understand more about the time course of treatment effects, given that some treatments may not produce lasting effects. Learning the limits might prompt research on booster sessions and periodic checkups to prevent relapses. There have been seven long-term follow-up studies to treatment studies that examined CBT for PTSD. Most of these studies have not extended assessment beyond one year, with the exception of three studies whose follow-up extended to five years. These longer follow-up periods are more representative of long-term efficacy, such that shorter periods may be insufficient to evaluate the durability of the therapeutic benefits. Given the small number of follow-up studies, each will be reviewed separately, including PE (the treatment with the most empirical support) and other CBTs. In general, these studies have found positive results with regard to maintenance of symptom improvement and long-term superiority of CBT. The following section reviews the long-term follow-up studies of CBT for PTSD.

Several studies have found that treatment gains from CBT for PTSD are maintained at follow-up. Echeburua and colleagues (1996) compared two therapeutic programs, cognitive restructuring/specific coping skills training and progressive muscle relaxation (PMR), across 20 patients in the treatment of acute PTSD in victims of sexual aggression. They found no differences at post-treatment. Additionally, both groups demonstrated a similar trajectory - rapid improvement between pre- and post-treatment, a slow increase in improvement between post-
treatment and six-month follow-up, and maintenance of changes onward. The cognitive restructuring/coping skills training condition was superior at the 12-month follow-up, suggesting that CBT for PTSD may be effective long-term. However, this study did not use all components of PE and is limited in its small sample size.

Similar maintenance with CBT was found by Neuner and colleagues (2004) in the first randomized clinical trial for traumatized survivors of war living in a developing country. The study consisted of 43 Sudanese refugees who fled from the civil war to Northern Uganda. The authors compared the efficacy of three treatment conditions: a) one session of psychoeducation (control group); b) four sessions of supportive counseling in addition to psychoeducation; and c) four sessions of narrative exposure therapy (NET), a short-term approach based on CBT and testimony therapy, which included psychoeducation. Assessments were conducted immediately after therapy, four months after therapy, and one year after therapy. At one year, the NET group had a significantly better outcome than the other two groups with regard to long-term change, indicating that the well-established efficacy of exposure techniques for the treatment of PTSD may apply long-term. However, this study is also limited in its small sample size and did not use all components of PE.

Foa and colleagues found across two studies that treatment gains were maintained over a one-year follow-up. The first study (Foa, Dancu, Hembree et al., 1999) examined treatment for 96 female victims of sexual and nonsexual assault with chronic PTSD. Patients were assigned to one of four conditions: stress inoculation training (SIT), PE, and SIT + PE, and waitlist control. Treatment consisted of 9 twice-weekly individual sessions, and evaluations were conducted at pretreatment, post-treatment, 3 months, 6 months, and 12-month follow-ups. All groups had a better outcome than the waitlist control group in reducing PTSD severity. Immediate effects
were maintained at 12-month follow-up in all three active treatments. The second study (Foa et al., 2005) compared the efficacy of PE alone with a program that combined PE and cognitive restructuring (CR). They examined whether additional sessions would enhance outcome for patients who did not reach an optimal response after 8 sessions. Treatment consisted of 9-12 sessions at the academic center or community clinic across 171 patients. Evaluations were conducted at pretreatment, post-treatment, 3 months, 6 months, and 12 months. Findings revealed that PE alone and PE/CR were superior to waitlist control in reducing PTSD and depression. Treatment gains were maintained at follow-up.

Tarrier and colleagues (1999) also examined the cognitive and exposure components of PTSD treatment. They tested the relative efficacy of cognitive therapy (excluding exposure) and imaginal exposure (excluding discussions of thoughts and emotions) among patients who had experienced a range of traumas. The outcome measures showed a significant improvement over treatment that was maintained at one-year follow-up, although there was no indication that one treatment was superior to the other. The findings suggest that clinical benefit and general treatment equivalence are maintained at one-year follow-up.

Finally, maintenance over follow-up was found in the Department of Veterans Affairs Cooperative Study (Schnurr, Friedman, Foy et al., 2003), a randomized clinical trial of two methods of group psychotherapy for treating PTSD in male Vietnam veterans. 360 Vietnam veterans were randomly assigned to receive trauma-focused group therapy (TFGT) or a present-centered group therapy (PCGT) comparison treatment. TFGT is a cognitive-behavioral treatment that included education about PTSD, coping resource assessment, self-management of symptoms, premilitary autobiographies, war zone scene identification, exposure, cognitive restructuring, and relapse prevention. PCGT focused on rapport, education about PTSD
symptoms and associated features, the connection between PTSD symptoms and difficulties in relationships and problem-solving, identification and clarification of individual members’ specific issues and means of dealing with these issues, and a review of experience and progress. Treatment was provided weekly to groups of six members for 30 weeks, followed by five monthly booster sessions. Follow-up assessments were conducted at the end of treatment (7 months) and at the end of booster sessions (12 months). Among the 325 patients in one or both follow-up assessments, PTSD severity was improved from baseline across both conditions.

**Five-year follow-ups.** With follow-up periods being typically 12 months or less, little is known about the long-term effects of these cognitive-behavioral treatments and whether the clinical benefits obtained at the end of treatment and over short-term follow-ups are sustained over longer periods. Only three studies consisted of follow-ups over a five-year period. One of these studies found a worsening of symptoms over the follow-up period (Macklin, Metzger, Lasko et al., 2000) of 13 Vietnam combat veterans with chronic PTSD who participated in a study of eye movement desensitization and reprocessing (EMDR). EMDR combines the principles of exposure therapy with rhythmic eye movements that are initiated and maintained by tracking a therapist’s lateral hand movements. Pretreatment and follow-up outcome measures were compared with those of a matched control group of 14 combat veterans with PTSD who did not receive EMDR. Results indicated that 10 weekly sessions of EMDR, although yielding some benefit, did not produce long-lasting improvement in the veterans’ PTSD symptoms. In general, the PTSD symptoms of treatment patients and control patients were worse five years after treatment than at the initial, pre-EMDR assessment. These findings suggest a poor expectation regarding the long-term benefits of treatment, although it may have been limited by small sample size and deviated from the typical cognitive-behavior treatment for PTSD.
The other two five-year follow-up studies found maintenance of treatment gains. Tarrier and Sommerfield (2004) recontacted subjects who were in an earlier clinical trial (Tarrier, Pilgrim, Sommerfield et al., 1999) and assessed their status five years later. That is, the authors examined whether the clinical gains after treatment and at 12-month follow-up were maintained and whether exposure or cognitive therapy was superior at five-year follow-up. At five-year follow-up, the patients had maintained their gains, contrary to the results from Macklin and colleagues (2000). These contradictory results may be a function of differences in sample characteristics (e.g., veterans versus civilians) or type of therapy (e.g., EMDR versus cognitive therapy/exposure therapy). In this study, results revealed minimal clinical deterioration after five years, such that few patients received a PTSD diagnosis at this assessment.

Similar findings were revealed in long-term follow-up assessment of patients from a randomized controlled trial (RCT) comparing cognitive processing therapy (CPT) with prolonged exposure for PTSD, with the goal of examining long-term outcomes among all patients who were randomized in the original trial (Resick, Williams, Suvak et al., 2012). Of the 171 patients in the original trial, 126 were located and reassessed. In the original trial (Resick et al., 2002), patients receiving either CPT or PE showed marked improvements in PTSD and depression from pretreatment to post-treatment. Results revealed a strong maintenance of treatment gains throughout the follow-up period. Overall, 85% of patients who were randomized to one of the two brief treatments reported clinically reliable improvements at long-term follow-up. This study suggests that treatment improvements of PTSD symptoms and diagnosis are long-lasting.

Follow-up studies have been done on RCTs for several different types of cognitive-behavioral treatments for PTSD, including narrative exposure therapy, PE, trauma-focused group
therapy, EMDR, and cognitive processing therapy. Based on the limited number of follow-up studies, there is clearly a dearth of literature on long-term outcomes of PTSD treatment with large samples, particularly for studies using PE. Results from the aforementioned studies suggest that treatment improvements with CBT of PTSD symptoms and diagnosis might be long-lasting. However, one study found a rebound effect in PTSD symptoms after treatment was discontinued. Additionally, most follow-up assessments in CBT trials have been relatively short (one year or less). Therefore, the long-term impact of CBT on PTSD remains unclear. It will be important to conduct long-term follow-up studies with large samples that include a range of ethnic diversities and different types of trauma to determine the long-term efficacy of CBT for PTSD.

Treatment for Comorbid PTSD and Substance Use Disorders

Many studies have encompassed alcohol dependence under substance use disorders (SUD). Despite the high co-occurrence between PTSD and SUD, understanding of treatment for this comorbid population is limited. Many RCTs for PTSD have used concurrent SUD as exclusion criteria. Although not empirically supported, this was based on belief that exposure is too emotionally distressing for SUD patients who are already vulnerable (Abueg & Fairbank, 1992; Triffleman, Carroll, & Kellogg, 1999) and it may be difficult to tolerate exposure without relapse. It was also suggested that cognitive impairments among SUD patients might interfere with imaginal exposures (Abueg & Fairbank, 1992; Pitman, Altman, Greenwald et al., 1991). Therefore, the application and empirical investigation of efficacy of exposure therapy has been primarily limited to individuals without comorbid substance and alcohol use disorders.

Differences in clinical profiles between comorbid populations and PTSD or SUD only influence treatment outcomes (Ouimette, Finney, & Moos, 1999). Ouimette and colleagues (1999) examined the two-year post-treatment course among individuals who had received the 12-
step program, cognitive-behavioral therapy, or combination treatment (Ouimette, Finney, & Moos, 1997). Three populations were compared: a) patients with SUD and PTSD; b) patients with SUD only; and c) patients with SUD and other comorbid psychiatric diagnoses. Patients with SUD and PTSD had a poorer long-term course of substance use, psychological symptoms, and psychological outcomes than SUD only and SUD + other comorbid diagnoses.

A recent study highlights the importance of assessing and addressing both symptom domains among SUD/PTSD patients. Back and colleagues (2014) explored veterans’ perceptions of SUD/PTSD symptom interplay and treatment preferences. Almost all (94.3%) perceived a relationship between substance use and PTSD symptoms. Congruent with the self-medication hypothesis (Khantzian, 1985), individuals may use alcohol or drugs in an attempt to mitigate distressing symptoms (e.g., nightmares, intrusive trauma memories). Notably, only 11.4% of participants reported an improvement in PTSD symptoms secondary to decreased substance use, and many (56.5%) reported a worsening of PTSD symptoms secondary to decreased substance use. Given the high need for effective treatments in patients with comorbidity, evaluating the efficacy of treatments for this patient population is a high clinical priority.

A growing body of evidence is accumulating demonstrating the efficacy of imaginal exposure in reducing PTSD in patients with co-occurring substance or alcohol abuse. Van Dam and colleagues (2012) conducted a systematic review of psychological treatments for comorbid PTSD and substance use disorders. They identified 17 studies evaluating ten treatment protocols. Four were non-trauma focused, and six treatments were trauma-focused. Six studies were RCTs, eight were uncontrolled studies, and three were case studies. Ten studies showed significant reductions in PTSD and SUD symptoms for the experimental treatments. Two studies found significant symptom improvements for PTSD, but not SUD (Cook, Walser, Kane et al., 2006;
Hien, Wells, Jiang et al., 2009). One study reported symptom improvements for the sample as a whole, but did not specify results for the experimental treatment alone (Triffleman, 2000). The authors recommended that research directly compare trauma-focused versus non-trauma-focused interventions in order to draw conclusions regarding their relative efficacy for patients with comorbid PTSD and substance use disorders. Additionally, given the high dropout rates, the authors recommended research on safety issues and retention of patients in treatment. Finally, they indicated a strong need for long-term follow-up measurements to investigate the sustainability of treatment results over a longer period of time.

Brady and colleagues (2001) conducted a preliminary, uncontrolled evaluation of the safety, efficacy, and tolerability of exposure therapy in the treatment of PTSD among a sample of 39 individuals with comorbid PTSD and cocaine dependence. Therapy consisted of a combination of imaginal and in-vivo exposure therapy techniques to treat PTSD symptoms, and cognitive-behavioral techniques to treat cocaine dependence. Although dropout rate was high, treatment completers demonstrated reductions in all PTSD symptom clusters and reductions in cocaine use from baseline to end of treatment. They also demonstrated reductions in depressive symptomatology. These improvements maintained over a six-month follow-up among completers. Results from this study suggest that exposure therapy can be used safely and effectively in treatment of PTSD in some patients with cocaine dependence. The authors acknowledge limitations in the uncontrolled nature of the study, small number of subjects, and high dropout. Additionally, they note that the findings may not be generalizable to individuals with PTSD and other types of comorbid substance use disorders.

Najavits and colleagues (2005) addressed some of these limitations in conducting the first outcome trial to treat a sample of civilian men with PTSD and substance use disorders using a
manualized psychosocial treatment. The authors evaluated a combination treatment, Seeking Safety plus exposure therapy. Seeking Safety is an integrated cognitive-behavioral treatment of PTSD and substance abuse. Each session (12 total) covers a different topic, such as safety, taking back power from PTSD, knowing when substances are in control, honesty, setting boundaries in relationships, compassion, healing from anger, creating meaning, integrating the split self, taking good care of oneself, and detaching from emotional pain. In this pilot study, 5 patients were offered 30 sessions over five months with the option of selecting the extent of each treatment they preferred. Results revealed significant improvements in drug use, family/social functioning, trauma symptoms, anxiety, dissociation, sexuality, hostility, overall functioning, meaningfulness, and feelings and thoughts related to safety. In general, this study further provided evidence for using time-limited outpatient exposure therapy in a PTSD/SUD sample. The improvement in substance use suggests that when PTSD is adequately addressed, need for substances may diminish. The authors encouraged studies with greater methodological rigor (e.g., control condition, control over external treatments, follow-up data, and larger sample).

Triffleman (2000) conducted the first small controlled pilot study of the treatment of comorbid PTSD and substance abuse across 19 methadone maintained and primary-cocaine abusing patients. The treatments compared were a) Substance Dependence-Post-Traumatic Stress Disorder Therapy (SDPT), an integrated two-phase CBT which uses existing treatment techniques including coping skills treatment for addictions, stress inoculation therapy, and in-vivo exposure; and b) Twelve-Step Facilitation Therapy, a proxy for treatment as usual, that uses principles of 12-step programs as therapeutic techniques for induction and maintenance of substance abstinence. Improvement was demonstrated across the sample in PTSD severity, number of PTSD symptoms, addiction severity, and number of days using substances in the past
30 days. The authors note that the conclusions are limited by the small sample size and short duration of follow-up (one month post-treatment), particularly since PTSD and substance abuse are both chronic relapsing-remitting conditions for which maintenance therapies may prove useful. However, this study demonstrated that PTSD/SUD patients receiving exposure therapy are able to tolerate treatment.

Hien and colleagues (2009) compared the effectiveness of Seeking Safety to an active comparison health education group – Women’s Health Education (WHE). They randomized 353 women with full or subthreshold PTSD from any traumatic event and current diagnosis of substance/alcohol abuse or dependence to receive 12 sessions of Seeking Safety or WHE with follow-up at 1 week, 3 months, 6 months, and 12 months post-treatment. Results showed clinically significant reductions in clinician-administered and self-reported PTSD symptoms. Although there were no differences between the two conditions, and follow-up showed no significant change from baseline with regard to substance use, the results suggest that individuals with PTSD and comorbid substance use disorders can be successfully treated with exposure therapy, and that exposure therapy does not increase the risk for relapse.

Mills and colleagues (2012) examined whether an integrated treatment for PTSD and substance dependence, Concurrent Treatment of PTSD and Substance Use Disorders Using Prolonged Exposure (COPE), achieves greater reductions in PTSD and substance dependence symptom severity compared with usual treatment for substance abuse. The RCT included 103 participants who met DSM-IV-TR criteria for both PTSD and substance dependence. Participants were randomized to COPE plus usual treatment, or usual treatment alone. Reductions in PTSD symptom severity were found for both groups, but significantly higher
among those who received COPE plus usual treatment. No significant difference was found in relation to improvement in severity of substance dependence or substance use.

These studies represent a growing body of literature showing that concurrent treatment for comorbid PTSD and substance use disorders is viable. The authors from these studies recommend treating both disorders simultaneously instead of requiring substance abstinence before addressing trauma-related symptoms. Although the independent contributions of exposure therapy versus substance abuse treatment cannot yet be discerned given the scarcity of comparative research, the fact that symptoms of PTSD were improved in these studies suggests that a comorbid SUD diagnosis does not interfere with the treatment for PTSD.

**Treatment for Comorbid PTSD and Alcohol Dependence**

Since most research on PTSD and alcohol dependence (AD) is within the context of a broader category of substance use disorders, more data are needed to examine PTSD and alcohol dependence specifically. Additionally, although large-scale AD treatment studies have not excluded PTSD patients (Streeton & Whalen, 2001), they did not specifically explore the relation between AD and PTSD. Finally, although there are approved treatments for both, the efficacy of these treatments in this comorbid population is unclear.

Several studies have sought to examine the efficacy of treatments for patients with comorbid PTSD and alcohol dependence. Back and colleagues (2006) examined the temporal course of improvement in 94 patients with PTSD and AD participating in a 12-week study. Patients received weekly individual CBT based on the Project MATCH manual targeting AD (Kadden, Carroll, Donovan et al., 1995; Monti, Abrams, Kadden, & Cooney, 1989; Project MATCH Research Group, 1997). The CBT focused only on alcohol use symptoms and did not target PTSD symptoms. Additionally, patients were randomly assigned to sertraline or placebo to
target anxiety symptoms related to PTSD. Findings revealed that improvement in PTSD had a greater impact on improvement in AD symptoms than vice versa. Specifically, those who were PTSD responders drank less in quantity and frequency at the end of treatment compared with non-PTSD responders. Conversely, PTSD symptoms at the end of treatment were not different among alcohol treatment responders and non-responders. These findings suggest that co-occurring PTSD symptoms may have a strong effect on AD treatment outcome, and that PTSD treatment may be important in optimizing outcomes for patients with comorbid PTSD and AD. Therefore, an integrated therapy in which PTSD symptoms are targeted earlier in therapy may help reduce PTSD and alcohol use.

Kaysen and colleagues (2013) examined the extent to which cognitive processing therapy (CPT) is tolerated by and effective in treating PTSD symptoms for veterans with PTSD and AD, as compared to veterans with PTSD only in an outpatient treatment setting. Participants were categorized by the following diagnostic groups: a) current AD (past 12 months); b) past AD; and c) no AD. Participants completed an average of 9 sessions of CPT, with no significant difference between AD diagnostic groups on the number of CPT sessions completed. Results revealed no interactions between AD diagnosis and treatment outcome. That is, PTSD symptoms significantly improved over time, regardless of an AD diagnosis. These findings suggest that cognitive-behavioral therapy should be considered as a treatment option for individuals with PTSD and AD.

Exposure therapy was also examined in several studies of individuals with comorbid PTSD and AD. Coffey and colleagues (2006) randomly assigned 43 patients with PTSD and AD to either trauma-focused imaginal exposure or imagery-based relaxation. A cue reactivity paradigm was used to assess alcohol craving prior to and after completion of the six clinical
sessions. For study completers, PTSD symptoms, alcohol cravings, and distress elicited by trauma images decreased in the exposure condition but not the relaxation condition. Findings supported the hypothesis that negative emotion is a mechanism of alcohol craving and highlight the importance of negative emotion in the maintenance of alcohol dependence. Therefore, it may be important to target PTSD and AD simultaneously.

Sannibale and colleagues (2013) conducted an RCT with 62 adults with comorbid PTSD and alcohol dependence to examine the efficacy of integrated CBT. Participants were randomly assigned to integrated treatment for PTSD and AD or CBT for AD only. Individuals in both conditions received the same treatment targeting AD, which was based on the Project MATCH manual and the motivationally enhanced Combined Behavioral Intervention Manual (COMBINE). Participants in the integrated group also received exposure-based CBT for PTSD, and participants in the control group also received supportive counseling. Reductions in PTSD severity were evident in both groups; however, the integrated group exhibited a twofold greater rate of clinically significant change in PTSD severity at post-treatment than the latter group. Participants in the CBT for AD group exhibited larger reductions that the integrated group in alcohol consumption and dependence. Results lend support to a mutually maintaining effect between AD and PTSD, and suggest that individuals with these comorbid conditions can derive substantial benefit from CBT targeting both diagnoses.

Data are in support of a comprehensive treatment plan for patients with comorbid PTSD and alcohol dependence, such that treating both disorders simultaneously and effectively, despite a more complicated presentation, is possible. In contrast to original concerns about exposure therapy with AD patients, the aforementioned findings suggest that confronting trauma-related stimuli and coping with the associated emotions without alcohol may in fact weaken the relation
between negative emotions and alcohol use. Furthermore, findings from these studies highlight the interaction between PTSD and AD, and the impact that each may have on treatment outcome. Therefore, an integrated treatment in which both disorders are targeted may help improve PTSD and alcohol use. Although studies have examined concurrent treatments for comorbid PTSD and AD, none had previously examined whether concurrent treatment with naltrexone and PE produces greater and more persistent improvements in comorbid patients than either alone.

RCT of Comorbid PTSD and AD Using Naltrexone and Prolonged Exposure

The efficacy of an evidence-based treatment for alcohol dependence (naltrexone), an evidence-based treatment for PTSD (prolonged exposure therapy), their combination, and supportive counseling was compared in a randomized clinical trial for individuals with comorbid AD and PTSD (Foa et al., 2013). The study was conducted at the University of Pennsylvania and the Philadelphia Veterans Administration between 2001 and 2009, and the study reported in this manuscript represents an investigation of the long-term follow-up of its effects. Participants (N = 165) were randomly assigned to: 1) prolonged exposure therapy plus naltrexone (100 mg); 2) prolonged exposure therapy plus pill placebo; 3) supportive counseling plus naltrexone (100 mg); or 4) supportive counseling plus pill placebo.

The overall goal of the study was to determine if simultaneous treatment of PTSD and AD is more efficacious than treatment that addresses only one of the disorders. The sub-goals of the original study were as follows: a) determine the efficacy of naltrexone in reducing drinking in patients with comorbid PTSD; b) determine the efficacy of PE in reducing PTSD symptoms in patients with comorbid AD; c) determine the efficacy of treatment targeted at one disorder on the comorbid condition; and d) determine whether concurrent treatment with naltrexone and PE produces greater and more persistent improvements in comorbid patients than either alone. The
Timeline Follow-Back Interview and the PTSD Symptom Severity Interview were used to assess the percentage of days drinking alcohol and PTSD severity respectively. Independent evaluations occurred prior to treatment (week 0), at post-treatment (week 24), and six months after treatment discontinuation (week 52). More information is provided in the Method section on this study and the long-term follow-up study.

**Summary of findings from the RCT.** Among the 165 participants, 53 (32.1%) dropped out of the study prior to the end of the treatment period. This rate did not significantly differ across treatment groups. Twelve participants were removed from the study because of serious adverse events. There were no significant differences on demographic and pretreatment outcome variables across groups. On average, participants completed a mean of 6.18 (SD = 3.86) exposures sessions in the combination condition versus a mean of 6.48 (SD = 3.49) sessions in the PE only group. There were 141 participants (85%) who met criteria for adherence to medication and supportive counseling (defined as > 80% medication compliance and supportive counseling attendance) and differences between groups were not statistically significant.

**Drinking outcome.** Participants in all groups reported reductions in percent of days drinking during treatment. At post-treatment, a significant main effect of naltrexone emerged (mean difference = 7.93%, \( p < .01, d = .42 \)), such that patients receiving naltrexone had lower percent of days drinking than patients receiving placebo. At post-treatment, the main effect of PE and the interaction of naltrexone x PE were not statistically significant.

**PTSD outcome.** All four groups showed reductions in PTSD symptoms during the treatment period. The main effect of PE at post-treatment was not statistically significant (mean difference = 2.63, \( p = .15, d = .23 \)), nor was the main effect of naltrexone and the interaction of PE x naltrexone. The null finding is possibly explained by the fact that all participants received
supportive counseling, and that nonspecific factors involved in supportive counseling masked some of the unique effects of PE. In addition, attendance to PE sessions was lower in this study than in other trials of PE. Low adherence to therapy has been found in other studies of patients with PTSD and substance use disorders. For example, Hien and colleagues (2009) found that only 12.2% of patients completed all 12 sessions of the Seeking Safety treatment program. The authors of this RCT explain the low adherence to PE sessions by the multiple life difficulties experienced by participants (e.g., homelessness, health problems). However, findings indicated that PE was not associated with increased drinking, contradicting the common view that trauma-focused therapy is contraindicated for individuals with alcohol dependence and PTSD because it may exacerbate PTSD symptoms and thereby lead to increased alcohol use.

**Six-month follow-up.** Participants were assessed six months after treatment discontinuation. During the follow-up period (post-treatment to follow-up), participants who received PE retained low drinking levels, whereas participants who did not receive PE had a higher relapse rate. That is, a significant PE x Time interaction emerged ($p < .05$, $d = .41$), such that patients receiving PE had a mean change in percent of days drinking during follow-up of 3.6% (95% CI, -2.2% to 9.5%), which was not statistically significant, whereas patients not receiving PE exhibited a mean increase in percent of days drinking during follow-up of 15.9% (95% CI, 8.8% to 23.1%). The interactions of Naltrexone x Time ($p = .98$) and PE x Naltrexone x Time ($p = .39$) were not statistically significant during follow-up.

Participant PTSD severity slightly decreased across all treatment groups during the follow-up period. The interactions of PE x Time ($p = .55$), Naltrexone x Time ($p = .66$) and PE x Naltrexone x Time ($p = .63$) were not statistically significant for the follow-up period. However, in an exploratory analysis, 70% of participants in the combination group achieved a low level of
PTSD severity (< 10 on the PTSD Symptom Severity Interview) six months after treatment discontinuation versus 55% of participants in the PE only group, 43.9% in the naltrexone only group, and 37.2% in the supportive counseling group. Taken together, these findings during follow-up suggest that PE protects patients with AD and PTSD from relapse after treatment discontinuation.

**Statement of Problem**

As previously mentioned, little is known about the long-term effects of CBT on PTSD. Additionally, more research is needed on the long-term efficacy of naltrexone in patients with alcohol dependence, as there is some evidence that relapse is high after naltrexone is discontinued. Follow-up studies of initial clinical trials are important in providing information about the durability of improvement following discontinuation of treatment. Pharmacological and psychotherapy interventions that are initially beneficial may have rebound effects, which would suggest the need for extended treatment. Treatments are needed that will improve long-term prospects. Unfortunately, there is little research on the long-term effects of either monotherapy (naltrexone or PE) or combined treatment for the comorbid PTSD/AD population.

The present study is a long-term follow-up assessment conducted 5-10 years after the aforementioned randomized controlled trial that compared combined therapy (naltrexone + PE) with either naltrexone or PE alone for patients with PTSD and alcohol dependence (Foa et al., 2013). The goal is to examine long-term outcomes on measures of alcohol use and PTSD symptoms among participants in the original trial.

**Hypotheses**
**Hypothesis 1.** Reductions in PTSD symptoms between pretreatment and post-treatment will be maintained at long-term follow-up among those who received PE, but not those who did not receive PE.

**Hypothesis 2.** Reductions in drinking between pretreatment and post-treatment will be maintained at long-term follow-up among those who received naltrexone, but not those who received placebo.

**Hypothesis 3.** Reductions in drinking and PTSD symptoms between pretreatment and post-treatment will show greater maintenance at long-term follow-up among those who received combination treatment than those who received monotherapy (PE alone or naltrexone alone).
Method¹

Participants in the Original RCT

At enrollment in the original study, participants met DSM-IV criteria for alcohol dependence and PTSD following a trauma. Participants ranged in age from 18-65 years old, and reported heavy alcohol drinking in the past 30 days. Heavy drinking was defined as above 12 drinks per week, where each drink was 0.6 ounces of ethanol. All participants were required to agree to medical detoxification. Among the 657 individuals assessed for eligibility via telephone, 165 were randomized into the study (40 to PE + naltrexone, 40 to PE + placebo, 42 to naltrexone + supportive counseling, and 43 to supportive counseling + placebo). Among those, 112 received intervention as randomized (others did not respond or withdrew, had serious adverse events, or scheduling conflicts). A total of 86 individuals participated in the 6-month follow-up.

Exclusion criteria included: a) current DSM-IV diagnosis of any substance dependence other than alcohol, nicotine, or cannabis in the past 30 days; b) serious medical illness; c) current severe psychiatric symptoms (e.g., psychosis); d) pregnancy or nursing, or no use of reliable contraception; e) significant risk of serious violent behavior during the past year; f) trauma consisted of an assault by an intimate partner with whom there was a continuing intimate relationship. Antidepressant medications such as SSRIs were permitted; however, participants who reported recent changes to psychiatric medication were not seen until a sufficient amount of time had passed so that their regimen was stable (8-12 weeks).

Procedures for the Original RCT

Recruitment and intake procedures. Recruitment was accomplished through frequent advertising in local newspapers, outreach activities to community agencies, and professional

¹ Methods of the original study are adapted from Foa & Williams (2010).
referrals to the Translational Research Center (TRC) and the Center for the Treatment and Study of Anxiety (CTSA). Both clinics are housed at the University of Pennsylvania Department of Psychiatry and serve the greater Philadelphia metropolitan area. The CTSA has developed a network of referrals in Philadelphia and its vicinity, including trauma victim organizations (e.g., Women Organized Against Rape, victims assistance agencies, Victim Assistance Officers in the Philadelphia Police Department), the Red Cross, emergency rooms, victim compensation organizations, and private medication and mental health practices. Outreach and advertising efforts instructed prospective patients to contact the Intake Coordinator, who screened individuals to assess eligibility.

**Study entry procedures.** Eligible participants provided informed consent to participate in the study, and comprehension of the consent form was evaluated with a quiz. Participants then completed outpatient medical detoxification of at least three consecutive days of abstinence from alcohol, assessed through self-reports and breathalyzer levels, which included visits to the nurse for three to seven days of medical monitoring.

**Assessment.** Measures for assessing alcohol use and PTSD were administered at various time points. The Timeline Follow-Back Interview (TLFB), a semi-structured interview assessing daily alcohol use, was administered at baseline (immediately prior to the start of treatment), weekly during weeks 1-12, biweekly during weeks 14-22, and at weeks 24 (post-treatment), 38 (three-month post-treatment follow-up), and 52 (six-month post-treatment follow-up). The PTSD Symptom Scale Interview (PSS-I), a clinical interview that evaluates DSM-IV PTSD symptoms on a frequency/severity scale, was administered at baseline, monthly during weeks 4-20, and at weeks 24, 38, and 52. Other alcohol, PTSD, psychopathology, and treatment assessment
measures were included in the original study, but are not described due to their exclusion from the long-term follow-up study.

**Treatment procedures.** Patients were randomly assigned to naltrexone or placebo, and PE or no PE. There was no active control condition for the PE arm, although patients in the PE waitlist control group were offered a course of PE if their PTSD symptoms did not improve. These interventions are described in detail below.

**Therapy arm.** The PE condition consisted of 12 weekly 1.5 to 2 hour sessions, followed by six biweekly sessions. Each PE session began with a review of the homework assignment and presentation of the agenda for that session, and ended with assignment of homework. The first two sessions of PE were devoted to gathering information about the trauma, education about common reactions to trauma, breathing retraining, presentation of the rationale for PE, and development of an in-vivo exposure hierarchy for homework assignments. The remaining sessions consisted of imaginal revisiting of the trauma memory and discussion of in-vivo exposure activities. Following each imaginal exposure, the therapist processed with the patient his or her thoughts and feelings about the experience, and, if necessary, instituted relaxation to help the patient manage anxiety. The final session of PE was devoted to terminating the treatment program. It involved reviewing progress and discussing the applications of treatment principles to daily life, including how to manage continuing urges to drink and potential lapses in abstinence as well as temporary increases in PTSD symptoms. A detailed description of PE can be found in the therapist manual (Foa, Hembree, & Rothbaum, 2007).

**Medication arm.** On the first three days of treatment, patients were given one 50 mg tablet of naltrexone or placebo, paired with one 100 mg riboflavin tablet to monitor adherence. On the fourth day, the dose increased to two 50 mg tablets of naltrexone or placebo, along with
the riboflavin tablet. Thus, for the remainder of the study, patients were asked to take three tablets once daily in the morning (two naltrexone/placebo and one riboflavin). The single-dose schedule was to enhance adherence (Cramer, Mattson, Prevey et al., 1989).

Liver enzymes were monitored at pretreatment and every four weeks during the trial. Nalrexone can also produce temporary side effects such as abdominal pain and headache (Guardia et al., 2002). For patients unable to tolerate side effects, dosage was reduced to 50 mg/day, and the patient was returned to 100 mg at the research physician’s discretion. Patients who could not tolerate a 50 mg dose were removed from the trial. Although all patients were instructed to take the medication once a day in the morning, modest changes in the regimen were permitted if it encouraged adherence.

Adherence with the dosing regimen was monitored by pill counts and urine riboflavin. In addition, the blood specimen taken at one month was analyzed for naltrexone and beta-naltrexol. These results were evaluated after the blind was broken to determine compliance and assess the relationship of naltrexone levels to pill counts and urine riboflavin measures.

**BRENDA.** All patients received a medication adherence enhancement intervention in the context of medical management using the BRENDA intervention. BRENDA is a biopsychosocial strategy for use in primary care settings (Volpicelli, Pattinati, McLellan, & O’Brien, 2001), combining standard medication management with compliance enhancement techniques based on motivational interviewing (Miller & Rollnick, 2001). The use of BRENDA with naltrexone for AD has been successful at the TRC and the University of Pennsylvania (Pettinati, Volpicelli, Pierce, & O’Brien, 2002), with positive effects on both treatment retention and medication compliance.

BRENDA consisted of 18 visits of 30 minutes with the study nurse. The nurse dispensed
medication, monitored adherence, and provided education about alcohol dependency, supportive counseling, and direct advice concerning drinking. Visits took place weekly during the first three months of the trial and biweekly during the remaining three months. Patients were encouraged to call the nurse or physician between visits with questions or concerns. The physician regularly reviewed all patient data. If the patient reported an adverse event to any of the project staff, including exacerbation of PTSD symptoms, the research physician followed up with the patient and appropriate clinical services were provided as indicated.

**Participants and Procedures for the Present Follow-Up**

The Institutional Review Board (IRB) of the University of Pennsylvania provided approval for the present follow-up study. The primary exclusion criterion was that participants discontinued treatment prior to week 24 (post-treatment) and did not participate in any assessments thereafter. Although the original plan was to conduct an intent-to-treat (ITT) analysis with all randomized participants, the challenges of tracking this population (e.g., many phone numbers were no longer in service and many participants could not be located) became clear upon beginning recruitment. Therefore, the goal was changed to targeting the participants who had remained involved to some extent in the original study. Results of tracking are described below in the Results section. The first step involved calling all eligible participants with the phone number they provided for themselves or a collateral during the study. Participants whose email addresses had been provided in the original study were emailed if they were not reachable by phone. Voicemails were also left for participants whose outgoing voicemail message identified themselves. Each participant was called four times at varying days and times. The next step involved using the participant’s social security number provided in the original study to locate their current phone numbers. Multiple public record databases were used to
identify the most up-to-date phone number, along with cellular telephone numbers. Finally, attempts were made to locate participants through Google searches and other social media networks.

The author conducted evaluations via telephone. Those who answered were told about the study and asked if they were interested in participating (see Appendix A for phone script). If so, they were given the option to do the interview then or schedule for a more convenient time. At the beginning of each interview, the participants were read the consent form and provided verbal consent, signed by the author (see Appendix A for consent form). They were then administered the PTSD, trauma, and alcohol measures (described below). If they endorsed a trauma since participation in the original study on the Traumatic Life Events Questionnaire, participants were asked to provide separate ratings on the PSS-I for their index trauma from the original study and their newer trauma to help them differentiate the two. The author was intensively trained in administering the measures by CTSA faculty. Training consisted of reading the administration manuals, listening to audiotapes of interviews while rating and comparing ratings to the originals, and completing evaluations while observed by CTSA faculty. The author attended weekly meetings during training to ensure reliability and discuss problems and questions that arose. The author was blind to treatment condition and outcome.

**Measures**

The PTSD Symptom Scale Interview (PSS-I; Foa, Riggs, Dancu, & Rothbaum, 1993) is a 17-item semi-structured interview that can be administered by interviewers who are trained to recognize the clinical picture presented by traumatized individuals. Each item corresponds to one of the 17 DSM-III-R diagnostic criteria for PTSD. The severity over the last 2 weeks of each item on the PSS-I is rated by the interviewer using a 4-point scale: 0 = not at all, 1 = a little bit, 2
= somewhat, 3 = very much. The total severity score is calculated as the sum of the severity ratings for the 17 items, and was used as the dependent variable in the present study. Parallel to the DSM-III-R, the items of the PSS-I are clustered into re-experiencing, avoidance, and hyperarousal. Studies have demonstrated satisfactory internal consistency, high test-retest reliability, and good concurrent validity (Foa et al., 1993). The PSS-I is included in Appendix B.

The Timeline Follow-Back Interview (TLFB; Sobell & Sobell, 1995) is procedure to aid recall of past drinking. It asks respondents to provide retrospective estimates of their daily drinking over a specified time period. The TLFB was used in the original study and present study to calculate the percentage of days drinking and percentage of heavy drinking days (> 4 drinks in a day) in the 90 days prior to assessment. Several memory aids including a calendar format are used to enhance recall (Sobell & Sobell, 1992, 1996). Since its development, the TLFB has been extensively evaluated in a variety of settings, over varying reporting intervals, and with diverse drinker populations, and has been found to have very good measurement properties (Sobell & Sobell, 1992). Instructions for administering the TLFB are included in Appendix C.

The Alcohol Use Disorders Identification Test (AUDIT; Saunders, Aasland, Babor et al., 1993) was developed from a six-country World Health Organization (WHO) collaborative project as a screening instrument for hazardous and harmful alcohol consumption. It is a 10-item questionnaire, which covers the domains of alcohol consumption, drinking behavior, and alcohol-related problems. Responses to each question are scored from 0-4, giving a maximum possible score of 40. In previous studies, among those diagnosed as having hazardous or harmful alcohol use, 92% had an AUDIT score of 8 or more, and 94% of those with non-hazardous consumption had a score of less than 8 (Saunders et al., 1993).
The Traumatic Life Events Questionnaire (TLEQ; Kubany, Leisen, Kaplan et al., 2000) is a 23-item self-report measure of 22 types of potentially traumatic events including natural disasters, exposure to warfare, robbery involving a weapon, physical abuse, and being stalked. For each event, respondents are asked to provide the number of times it occurred (ranging from “never” to “more than 5 times”) and whether fear, helplessness, or horror was present (“yes/no”). In studies with college students, Vietnam veterans, battered women, and residents of a substance abuse program, most items possessed adequate to excellent temporal stability (Kubany et al., 2000). The TLEQ is included in Appendix D.
Results

Results of Tracking

Attempts were made to contact 120 participants from the original sample (all except those who dropped before week 24 without any subsequent follow up). Among those, contact was never established with 86 (primarily due to out of service phone numbers and new phone numbers inaccessible by internet), and 11 had died. Of the remaining four individuals of which contact was established, three did not answer their phone at the scheduled assessment time or subsequently, and one denied having participated in the original study. The final sample for the long-term follow-up study included 19 participants who were assessed 5-10.5 years post-treatment, which represents 12% of the original sample and 22% of the six-month follow-up sample. See Figure 1 for a flow chart from the original study through long-term follow-up (LTFU)
Figure 1. Participant Flow Chart
Sample Differences

**LTFU versus non-LTFU participants.** In the entire original randomized sample, 24% were randomized to combination therapy, 24% to PE only, 26% to naltrexone only, and 26% to the control group. Among the long-term follow-up sample, 26% were from the combination group (n = 5), 16% from PE only (n = 3), 26% from naltrexone only (n = 5), and 32% from the control group (n = 6). A chi-square test revealed that the representation across treatment groups was not significantly different between the original and LTFU samples, $\chi^2(3, N = 165) = .93, p = .82$. Differences between participants and non-participants in the long-term follow-up study are presented in Table 1. There was a significant difference between the groups in time of treatment dropout (44% of non-participants dropped before week 24 compared to 5% of LTFU participants), number of BRENDA sessions completed (LTFU M = 14.11, SD = 3.21; Non-LTFU M = 11.83, SD = 4.96), and medication compliance (LTFU M = 95.84, SD = 8.97; Non-LTFU M = 86.03, SD = 27.67). There were marginal differences on gender (63% male in the non-participating sample, 84% male in the participating sample) and race/ethnicity (64% of non-participants were African-American compared to 58% participants; 29% of non-participants were Caucasian compared to 37% participants; 5% of non-participants were Hispanic compared to 0% participants; and 0% of non-participants were Native American compared to 5% participants). There were no differences between the two groups on employment status at baseline, age at baseline, baseline PSS-I and drinking scores, number of PE sessions attended, and post-treatment PSS-I and drinking scores.
Table 1

Differences Between Follow-Up and Non-Follow-Up Participants

<table>
<thead>
<tr>
<th>Variable</th>
<th>N</th>
<th>df</th>
<th>$\chi^2$</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>165</td>
<td>1</td>
<td>3.34</td>
<td>&lt;.10</td>
</tr>
<tr>
<td>Race/Ethnicity</td>
<td>165</td>
<td>4</td>
<td>9.27</td>
<td>&lt;.10</td>
</tr>
<tr>
<td>Employment status at baseline</td>
<td>164</td>
<td>4</td>
<td>1.2</td>
<td>0.88</td>
</tr>
<tr>
<td>Time of dropout</td>
<td>165</td>
<td>6</td>
<td>13.13</td>
<td>&lt;.05</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Variable</th>
<th>163</th>
<th>1</th>
<th>-0.53</th>
<th>0.6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>163</td>
<td>-0.63</td>
<td>0.53</td>
<td></td>
</tr>
<tr>
<td>% days drinking at BL</td>
<td>163</td>
<td>0.67</td>
<td>0.5</td>
<td></td>
</tr>
<tr>
<td>% heavy days drinking at BL</td>
<td>156</td>
<td>-1.35</td>
<td>0.18</td>
<td></td>
</tr>
<tr>
<td>PSS-I score at BL</td>
<td>78</td>
<td>-0.96</td>
<td>0.34</td>
<td></td>
</tr>
<tr>
<td>Number PE sessions</td>
<td>30.51</td>
<td>-2.7</td>
<td>&lt;.05</td>
<td></td>
</tr>
<tr>
<td>Number BRENDA sessions*</td>
<td>75.75</td>
<td>-3.19</td>
<td>&lt;.01</td>
<td></td>
</tr>
<tr>
<td>Medication Compliance*</td>
<td>119</td>
<td>-0.82</td>
<td>0.41</td>
<td></td>
</tr>
<tr>
<td>% days drinking at post-tx</td>
<td>119</td>
<td>-1.06</td>
<td>0.29</td>
<td></td>
</tr>
<tr>
<td>% days heavy drinking at post-tx</td>
<td>110</td>
<td>-1.08</td>
<td>0.28</td>
<td></td>
</tr>
<tr>
<td>PSS-I score at post-tx</td>
<td>110</td>
<td>-1.08</td>
<td>0.28</td>
<td></td>
</tr>
</tbody>
</table>

Note: BL = baseline; tx = treatment; * = equal variances not assumed

Characteristics by treatment condition. Characteristics of LTFU participants are presented in Table 2 by total sample and treatment condition. The groups did not differ significantly on gender, baseline employment status, ethnicity, percent of heavy drinking days at baseline, AUDIT scores at LTFU, or number of traumas resulting in PTSD since the original study. They differed significantly on baseline age, $F(3,15) = 7.35, p < .01$, and marginally on percent of days drinking at baseline, $F(3,15) = 2.86, p < .01$. That is, baseline ages in the combination and supportive counseling groups were significantly lower than the naltrexone only and PE only groups, and percent of days drinking was higher in the PE only and supportive counseling groups than the combination and naltrexone only groups.
Table 2

**Characteristics of the Follow-Up Sample**

<table>
<thead>
<tr>
<th></th>
<th>Total Sample</th>
<th>PE + NAL</th>
<th>PE Only</th>
<th>NAL Only</th>
<th>SC</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics</strong></td>
<td>(n = 19)</td>
<td>(n = 5)</td>
<td>(n = 3)</td>
<td>(n = 5)</td>
<td>(n = 6)</td>
</tr>
<tr>
<td>Age (M, SD)</td>
<td>43.8 (12.4)</td>
<td>33.4 (10.53)</td>
<td>52.33 (8.39)</td>
<td>55.8 (4.55)</td>
<td>38.33 (9.61)</td>
</tr>
<tr>
<td>Sex (n, %)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>3 (16)</td>
<td>1 (20)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>2 (33)</td>
</tr>
<tr>
<td>Male</td>
<td>16 (84)</td>
<td>4 (80)</td>
<td>3 (100)</td>
<td>5 (100)</td>
<td>4 (67)</td>
</tr>
<tr>
<td>Ethnicity (n, %)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>11 (58)</td>
<td>2 (40)</td>
<td>3 (100)</td>
<td>3 (60)</td>
<td>3 (50)</td>
</tr>
<tr>
<td>White</td>
<td>7 (37)</td>
<td>3 (60)</td>
<td>0 (0)</td>
<td>2 (40)</td>
<td>2 (33)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Native Am</td>
<td>1 (5)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (17)</td>
</tr>
<tr>
<td>Other</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Employment (n, %)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not working</td>
<td>8 (42)</td>
<td>3 (60)</td>
<td>1 (33.3)</td>
<td>3 (60)</td>
<td>1 (17)</td>
</tr>
<tr>
<td>Part-time</td>
<td>3 (16)</td>
<td>1 (20)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>2 (33)</td>
</tr>
<tr>
<td>Full-time</td>
<td>4 (21)</td>
<td>0 (0)</td>
<td>1 (33.3)</td>
<td>1 (60)</td>
<td>2 (33)</td>
</tr>
<tr>
<td>Disability</td>
<td>3 (16)</td>
<td>1 (20)</td>
<td>1 (33.3)</td>
<td>1 (60)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Student</td>
<td>1 (5)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (17)</td>
</tr>
<tr>
<td>Baseline drinking (M, SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% drinking days</td>
<td>78.27 (23.09)</td>
<td>68.67 (24.39)</td>
<td>94.01 (9.43)</td>
<td>62.56 (26.57)</td>
<td>91.50 (12.07)</td>
</tr>
<tr>
<td>% heavy drinking days</td>
<td>63.07 (29.40)</td>
<td>57.11 (29.12)</td>
<td>94.01 (9.43)</td>
<td>50.50 (28.20)</td>
<td>63.02 (31.53)</td>
</tr>
<tr>
<td>AUDIT score (M, SD)</td>
<td>12.32 (10.17)</td>
<td>15.40 (11.76)</td>
<td>17.67 (15.70)</td>
<td>4.40 (4.98)</td>
<td>13.67 (7.17)</td>
</tr>
<tr>
<td># subsequent traumas (M, SD)</td>
<td>.53 (.84)</td>
<td>.40 (.55)</td>
<td>1.33 (1.53)</td>
<td>.60 (.89)</td>
<td>.17 (.41)</td>
</tr>
</tbody>
</table>

*Note. PE = prolonged exposure; NAL = naltrexone; SC = supportive counseling*
**Surviving versus deceased.** Differences between the deceased and surviving groups were compared using chi-square analyses; results are presented in Table 3. There were no differences on treatment condition, gender, race/ethnicity, time dropped after enrollment, baseline and post-treatment drinking and PSS-I scores, or age. There was a significant difference on employment status at baseline. In the deceased group, 80% were not working or on disability, 20% were working part-time, and none were working full-time; in the surviving group, 61% were not working or on disability, 14% were working part-time, 22% were working full-time, and 3% were students.

Table 3

*Differences Between Deceased and Surviving Participants*

<table>
<thead>
<tr>
<th>Variable</th>
<th>N</th>
<th>df</th>
<th>$\chi^2$</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment Condition</td>
<td>165</td>
<td>3</td>
<td>1.19</td>
<td>0.76</td>
</tr>
<tr>
<td>Gender</td>
<td>165</td>
<td>1</td>
<td>0.28</td>
<td>0.84</td>
</tr>
<tr>
<td>Race/Ethnicity</td>
<td>165</td>
<td>4</td>
<td>1.76</td>
<td>0.78</td>
</tr>
<tr>
<td>Employment status at baseline</td>
<td>164</td>
<td>4</td>
<td>11.24</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>Time of dropout</td>
<td>165</td>
<td>6</td>
<td>3.26</td>
<td>0.76</td>
</tr>
<tr>
<td>Age</td>
<td>163</td>
<td></td>
<td>0.29</td>
<td>0.77</td>
</tr>
<tr>
<td>% days drinking at BL</td>
<td>163</td>
<td></td>
<td>0.85</td>
<td>0.4</td>
</tr>
<tr>
<td>% heavy days drinking at BL</td>
<td>163</td>
<td></td>
<td>1.22</td>
<td>0.23</td>
</tr>
<tr>
<td>PSS-I score at BL</td>
<td>156</td>
<td></td>
<td>0.27</td>
<td>0.79</td>
</tr>
<tr>
<td>% days drinking at post-tx</td>
<td>119</td>
<td></td>
<td>-1.3</td>
<td>0.9</td>
</tr>
<tr>
<td>% heavy days drinking at post-tx</td>
<td>119</td>
<td></td>
<td>-0.9</td>
<td>0.93</td>
</tr>
<tr>
<td>PSS-I score at post-tx</td>
<td>110</td>
<td></td>
<td>-0.22</td>
<td>0.83</td>
</tr>
</tbody>
</table>

*Note.* BL = baseline; tx = treatment
Outcomes Over Time

A series of mixed ANCOVAs were conducted to assess whether participants maintained their post-treatment gains in PTSD symptoms and drinking behaviors 5-10 years after treatment discontinuation (after controlling for time since treatment), and whether maintenance varied by treatment received in the original study. For each outcome variable, a 3 (pretreatment vs. post-treatment vs. LTFU) x 2 (naltrexone vs. placebo) x 2 (PE vs. no PE) analysis was conducted, with assessment points serving as a within-subject variable and the two treatments as between subject variables. Simple and repeated effects contrasts were computed to compare scores on the dependent variables between pretreatment and post-treatment, pretreatment and LTFU, and post-treatment and LTFU. This allowed for a more detailed analysis of statistically significant ANCOVA models. Bonferroni corrections were used to account for multiple comparisons. The dependent variables were scores on the PSS-I, percent of days drinking over the last 90 days, and percent of heavy drinking days over the past 90 days. Time since treatment was entered as a covariate (Tabachnick & Fidell, 2007). The assumptions of independent observations, normality, and sphericity were tested for each model. All three assumptions were met for the PSS-I and percent of heavy drinking days, but the sphericity assumption was violated for the percent of days drinking. Therefore, the Greenhouse-Geisser correction was used for these results.

Long-term PTSD outcomes. As can been seen in Table 5, PTSD severity varied by time, $F(2,26) = 3.32, p < .05$, partial $\eta^2 = 0.2$. Participants experienced significant reductions in PTSD symptoms between pretreatment and post-treatment, Time $F(1,13) = 10.28, p < .01$, partial $\eta^2 = .44$, and generally maintained their gains between post-treatment and LTFU, $F(1,13) = .48, p = .50$, partial $\eta^2 = .01$. 
**Treatment effects.** PTSD symptom severity over time was influenced by which treatment participants received, Time x Nal x PE $F(2,26) = 7.42, p < .01$, partial $\eta^2 = .36$. As can be seen in Table 4, all four groups had reduced PTSD symptoms at post- compared to pretreatment. However, the PTSD outcomes were maintained between post-treatment and LTFU only for the combination (PE + Nal) and control (PBO + no PE) conditions (see Table 4). On the other hand, PTSD severity significantly increased between post-treatment and LTFU in the monotherapy conditions (Nal + no PE and PE + PBO), such that PTSD levels at LTFU in the monotherapy conditions were statistically similar to pretreatment PTSD levels.

Table 4

**Means and Standard Deviations for PSS-I Across Time Points**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Pretreatment (wk 0)</th>
<th>Post-Treatment (wk 24)</th>
<th>Long-Term Follow-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medication</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Naltrexone</td>
<td>30.67 (7.35)</td>
<td>13.33 (9.61)</td>
<td>16.78 (13.35)</td>
</tr>
<tr>
<td>Placebo</td>
<td>29.22 (7.90)</td>
<td>16.22 (9.80)</td>
<td>17.00 (11.64)</td>
</tr>
<tr>
<td>Therapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prolonged Exposure</td>
<td>28.63 (7.44)</td>
<td>10.13 (6.47)</td>
<td>15.88 (12.44)</td>
</tr>
<tr>
<td>No PE</td>
<td>31.00 (7.66)</td>
<td>18.50 (10.21)</td>
<td>17.70 (12.53)</td>
</tr>
<tr>
<td>Condition</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PE + Nal</td>
<td>28.00 (6.29)$^a$</td>
<td>9.80 (5.63)$^b$</td>
<td>7.80 (7.09)$^b$</td>
</tr>
<tr>
<td>Nal + No PE</td>
<td>34.00 (8.04)$^a$</td>
<td>17.75 (12.53)$^b$</td>
<td>28.00 (10.30)$^a$</td>
</tr>
<tr>
<td>PE + PBO</td>
<td>29.67 (10.60)$^a$</td>
<td>10.67 (9.07)$^b$</td>
<td>29.33 (2.52)$^a$</td>
</tr>
<tr>
<td>PBO + No PE</td>
<td>29.00 (7.40)$^a$</td>
<td>19.00 (9.63)$^b$</td>
<td>10.83 (8.80)$^b$</td>
</tr>
<tr>
<td>Total</td>
<td>30.42 (7.52)$^a$</td>
<td>14.78 (9.53)$^b$</td>
<td>16.37 (12.02)$^{a,b}$</td>
</tr>
</tbody>
</table>

*Note.* PE = Prolonged Exposure; Nal = Naltrexone; PBO = Placebo

Different superscripts denote significant differences between time points
Table 5

Mixed ANCOVA for PSS-I Scores

<table>
<thead>
<tr>
<th>Variable</th>
<th>df</th>
<th>MS</th>
<th>F</th>
<th>p</th>
<th>partial eta&lt;sup&gt;2&lt;/sup&gt;</th>
<th>observed power</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Main Effects</strong></td>
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</tr>
<tr>
<td>Time Point</td>
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<td>190.46</td>
<td>3.32</td>
<td>&lt;.05</td>
<td>0.2</td>
<td>0.58</td>
</tr>
<tr>
<td>Naltrexone</td>
<td>1</td>
<td>2.69</td>
<td>0.03</td>
<td>0.88</td>
<td>0</td>
<td>0.05</td>
</tr>
<tr>
<td>Prolonged Exposure</td>
<td>1</td>
<td>192.6</td>
<td>1.77</td>
<td>0.21</td>
<td>0.12</td>
<td>0.23</td>
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<tr>
<td><strong>Interactions</strong></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time x PE</td>
<td>2</td>
<td>62.2</td>
<td>1.09</td>
<td>0.35</td>
<td>0.08</td>
<td>0.22</td>
</tr>
<tr>
<td>Time x Nal</td>
<td>2</td>
<td>13.21</td>
<td>0.23</td>
<td>0.8</td>
<td>0.02</td>
<td>0.08</td>
</tr>
<tr>
<td>Time x Nal x PE</td>
<td>2</td>
<td>425.58</td>
<td>7.42</td>
<td>&lt;.01</td>
<td>0.36</td>
<td>0.91</td>
</tr>
<tr>
<td><strong>Planned Contrasts</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Time</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-Tx vs. Post-Tx</td>
<td>1</td>
<td>729.26</td>
<td>10.28</td>
<td>&lt;.01</td>
<td>0.44</td>
<td>0.84</td>
</tr>
<tr>
<td>Pre-Tx vs. F/U</td>
<td>1</td>
<td>340.26</td>
<td>2.79</td>
<td>0.12</td>
<td>0.18</td>
<td>0.34</td>
</tr>
<tr>
<td>Post-Tx vs. F/U</td>
<td>1</td>
<td>73.25</td>
<td>0.48</td>
<td>0.5</td>
<td>0.04</td>
<td>0.1</td>
</tr>
<tr>
<td><strong>Time x PE x Nal</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-Tx vs. Post-Tx</td>
<td>1</td>
<td>11.91</td>
<td>0.17</td>
<td>0.69</td>
<td>0.01</td>
<td>0.07</td>
</tr>
<tr>
<td>Pre-Tx vs. F/U</td>
<td>1</td>
<td>1147.9</td>
<td>9.41</td>
<td>&lt;.01</td>
<td>0.04</td>
<td>0.12</td>
</tr>
<tr>
<td>Post-Tx vs. F/U</td>
<td>1</td>
<td>1394.68</td>
<td>9.22</td>
<td>&lt;.01</td>
<td>0.01</td>
<td>0.06</td>
</tr>
</tbody>
</table>

Note. PE = Prolonged Exposure; Nal = Naltrexone; Pre-Tx = Pretreatment; F/U = Follow-Up; Tx = Treatment

Percent of days drinking. As shown in Table 7, the percentage of days participants drank varied over time, \( F(1.35, 17.53) = 6.43, p < .05, \) partial \( \eta^2 = .33 \). Percent of drinking days significantly improved between pretreatment and post-treatment (see Table 6), \( F(1,13) = 9.32, p < .01, \) partial \( \eta^2 = .42 \), and these gains statistically maintained at LTFU, \( F(1,13) = 7.6 p < .05, \) partial \( \eta^2 = .37 \). The means in Table 6 reveals a moderate though not significant degree of relapse between post-treatment and LTFU, \( F(1,13) = 2.36, p = .15 \).

Treatment effects. Participants receiving naltrexone overall had lower percentage of days drinking, though this was not a treatment effect (e.g., it occurred at pretreatment and all timepoints), \( \text{Nal} F(1,13) = 7.26, p < .05, \) partial \( \eta^2 = .36 \) (Table 6). In fact, no treatment
differentially affected percent of days drinking, such that there were no interactions between time and treatment (see Table 7).

Table 6

Means and Standard Deviations for % Days Drinking Across Time Points

<table>
<thead>
<tr>
<th>Medication</th>
<th>Pretreatment (wk 0)</th>
<th>Post-Treatment (wk 24)</th>
<th>Long-Term Follow-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naltrexone</td>
<td>68.21 (24.21)</td>
<td>11.11 (19.60)</td>
<td>25.67 (35.33)</td>
</tr>
<tr>
<td>Placebo</td>
<td>92.33 (10.71)</td>
<td>17.86 (23.08)</td>
<td>54.22 (40.41)</td>
</tr>
<tr>
<td>Therapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prolonged Exposure</td>
<td>78.17 (23.18)</td>
<td>12.05 (20.64)</td>
<td>38.63 (40.76)</td>
</tr>
<tr>
<td>No PE</td>
<td>81.96 (22.11)</td>
<td>16.43 (22.28)</td>
<td>41.00 (40.90)</td>
</tr>
<tr>
<td>Condition</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PE + Nal</td>
<td>68.67 (24.39)</td>
<td>18.57 (24.54)</td>
<td>31.40 (38.51)</td>
</tr>
<tr>
<td>Nal + No PE</td>
<td>67.65 (27.73)</td>
<td>1.79 (3.57)</td>
<td>18.50 (35.03)</td>
</tr>
<tr>
<td>PE + PBO</td>
<td>94.01 (9.43)</td>
<td>1.19 (2.06)</td>
<td>50.67 (50.01)</td>
</tr>
<tr>
<td>PBO + No PE</td>
<td>91.50 (12.07)</td>
<td>26.19 (24.50)</td>
<td>56.00 (40.01)</td>
</tr>
<tr>
<td>Total</td>
<td>78.27 (23.09)(^a)</td>
<td>14.48 (21.06)(^b)</td>
<td>38.21 (39.26)(^b)</td>
</tr>
</tbody>
</table>

Note. PE = Prolonged Exposure; Nal = Naltrexone; PBO = Placebo

Different superscripts denote significant differences between time points.
Table 7

Mixed ANCOVA for Percent of Days Drinking

<table>
<thead>
<tr>
<th>Variable</th>
<th>df</th>
<th>MS</th>
<th>F</th>
<th>p</th>
<th>partial eta²</th>
<th>observed power</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Main Effects</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time Point</td>
<td>1.35</td>
<td>7212.45</td>
<td>6.43</td>
<td>&lt;.05</td>
<td>0.33</td>
<td>0.75</td>
</tr>
<tr>
<td>Naltrexone</td>
<td>1</td>
<td>1392.43</td>
<td>7.26</td>
<td>&lt;.05</td>
<td>0.36</td>
<td>0.7</td>
</tr>
<tr>
<td>Prolonged Exposure</td>
<td>1</td>
<td>0.37</td>
<td>0</td>
<td>0.97</td>
<td>0</td>
<td>0.05</td>
</tr>
<tr>
<td><strong>Interactions</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time x PE</td>
<td>1.35</td>
<td>88.33</td>
<td>0.08</td>
<td>0.92</td>
<td>0</td>
<td>0.06</td>
</tr>
<tr>
<td>Time x Nal</td>
<td>1.35</td>
<td>978.16</td>
<td>0.87</td>
<td>0.4</td>
<td>0.06</td>
<td>0.16</td>
</tr>
<tr>
<td>Time x Nal x PE</td>
<td>1.35</td>
<td>877.2</td>
<td>0.78</td>
<td>0.43</td>
<td>0.06</td>
<td>0.14</td>
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<tr>
<td><strong>Planned Contrasts</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-Tx vs Post-Tx</td>
<td>1</td>
<td>7030.99</td>
<td>9.32</td>
<td>&lt;.01</td>
<td>0.42</td>
<td>0.81</td>
</tr>
<tr>
<td>Pre-Tx vs. F/U</td>
<td>1</td>
<td>19163.87</td>
<td>7.6</td>
<td>&lt;.01</td>
<td>0.37</td>
<td>0.72</td>
</tr>
<tr>
<td>Post-Tx vs. F/U</td>
<td>1</td>
<td>2979.27</td>
<td>2.36</td>
<td>0.15</td>
<td>0.15</td>
<td>0.3</td>
</tr>
</tbody>
</table>

Note. PE = Prolonged Exposure; Nal = Naltrexone; Pre-Tx = Pretreatment; F/U = Follow-Up; Tx = Treatment

Percent of heavy drinking days. Results for percent of heavy drinking days were similar to percent of drinking days. As shown in Table 9, the percentage of heavy drinking days varied over time, Time $F(2,26) = 10.08$, $p < .001$, partial $\eta^2 = .44$. Percent of heavy drinking days significantly decreased between pretreatment and post-treatment (see Table 8), $F(1,13) = 7.51$, $p < .05$, partial $\eta^2 = .37$. However, the percent of heavy drinking days significantly increased between post-treatment and LTFU, $F(1,13) = 5.19$, $p < .05$, partial $\eta^2 = .29$, but still remained significantly lower at LTFU than at pretreatment, $F(1,13) = 13.89$, $p < .01$, partial $\eta^2 = .93$.

Treatment effects. As with percent of days drinking, participants who received naltrexone had an overall lower percentage of heavy days drinking, though this was not an effect of treatment, but rather a main effect of naltrexone, $F(1,13) = 5.15$, $p < .05$, partial $\eta^2 = .28$ (see Table 8 for means), and naltrexone did not influence percent of heavy drinking days over time,
Time x Nal $F(2,26) = 1.44, p = .26$, partial $\eta^2 = 0.1$. Percent of heavy drinking days over time was also not influenced by prolonged exposure treatment, Time x PE $F(2,26) = .51, p = .61$, partial $\eta^2 = .04$ or combination treatment, Time x Nal x PE $F(2.26) = .65, p = .53$, partial $\eta^2 = .05$.

**Table 8**

*Means and Standard Deviations for % Heavy Drinking Days Across Time Points*

<table>
<thead>
<tr>
<th></th>
<th>Pretreatment (wk 0)</th>
<th>Post-Treatment (wk 24)</th>
<th>Long-Term Follow-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Medication</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Naltrexone</td>
<td>55.21 (28.51)</td>
<td>6.75 (18.94)</td>
<td>15.00 (33.23)</td>
</tr>
<tr>
<td>Placebo</td>
<td>73.35 (29.72)</td>
<td>5.56 (12.89)</td>
<td>33.44 (23.57)</td>
</tr>
<tr>
<td><strong>Therapy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prolonged Exposure</td>
<td>70.95 (29.57)</td>
<td>7.59 (20.06)</td>
<td>29.00 (36.29)</td>
</tr>
<tr>
<td>No PE</td>
<td>58.95 (30.35)</td>
<td>6.15 (15.73)</td>
<td>20.40 (24.18)</td>
</tr>
<tr>
<td><strong>Condition</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PE + Nal</td>
<td>57.11 (29.11)</td>
<td>12.14 (25.20)</td>
<td>26.40 (42.91)</td>
</tr>
<tr>
<td>Nal + No PE</td>
<td>52.85 (31.99)</td>
<td>0.00 (0.00)</td>
<td>0.75 (1.50)</td>
</tr>
<tr>
<td>PE + PBO</td>
<td>94.01 (9.43)</td>
<td>0.00 (0.00)</td>
<td>33.33 (29.70)</td>
</tr>
<tr>
<td>PBO + No PE</td>
<td>63.02 (31.53)</td>
<td>8.33 (15.43)</td>
<td>33.50 (23.15)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>63.07 (29.40)$^a$</td>
<td>6.15 (15.73)$^b$</td>
<td>22.95 (29.22)$^c$</td>
</tr>
</tbody>
</table>

*Note. PE = Prolonged Exposure; Nal = Naltrexone; PBO = Placebo*

Different superscripts denote significant differences between time points.
Table 9

*Mixed ANCOVA for Percent of Heavy Drinking Days*

<table>
<thead>
<tr>
<th>Variable</th>
<th>df</th>
<th>MS</th>
<th>F</th>
<th>p</th>
<th>partial eta²</th>
<th>observed power</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Main Effects</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time Point</td>
<td>2</td>
<td>5501.49</td>
<td>10.08</td>
<td>&lt;.001</td>
<td>0.44</td>
<td>0.97</td>
</tr>
<tr>
<td>Naltrexone</td>
<td>1</td>
<td>837.86</td>
<td>5.15</td>
<td>&lt;.05</td>
<td>0.28</td>
<td>0.56</td>
</tr>
<tr>
<td>Prolonged Exposure</td>
<td>1</td>
<td>496.5</td>
<td>3.05</td>
<td>0.1</td>
<td>0.19</td>
<td>0.37</td>
</tr>
<tr>
<td><strong>Interactions</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time x PE</td>
<td>2</td>
<td>278.18</td>
<td>0.51</td>
<td>0.61</td>
<td>0.04</td>
<td>0.13</td>
</tr>
<tr>
<td>Time x Nal</td>
<td>2</td>
<td>785.34</td>
<td>1.44</td>
<td>0.26</td>
<td>0.1</td>
<td>0.28</td>
</tr>
<tr>
<td>Time x Nal x PE</td>
<td>2</td>
<td>356.68</td>
<td>0.65</td>
<td>0.53</td>
<td>0.05</td>
<td>0.15</td>
</tr>
<tr>
<td><strong>Planned Contrasts</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Time</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-Tx vs. Post-Tx</td>
<td>1</td>
<td>7796.01</td>
<td>7.51</td>
<td>&lt;.05</td>
<td>0.37</td>
<td>0.72</td>
</tr>
<tr>
<td>Pre-Tx vs. F/U</td>
<td>1</td>
<td>21721.63</td>
<td>13.89</td>
<td>&lt;.01</td>
<td>0.52</td>
<td>0.93</td>
</tr>
<tr>
<td>Post-Tx vs. F/U</td>
<td>1</td>
<td>3491.33</td>
<td>5.19</td>
<td>&lt;.05</td>
<td>0.29</td>
<td>0.56</td>
</tr>
</tbody>
</table>

*Note.* PE = Prolonged Exposure; Nal = Naltrexone; Pre-Tx = Pretreatment; F/U = Follow-Up; Tx = Treatment

**Effect Sizes**

Because of the limited statistical power for the important interaction effects (see above tables) conferred by the small sample size in the present study, the effect sizes of the changes between pretreatment and LTFU, and post-treatment and LTFU are provided for each outcome measure (Table 10). Effect sizes for pretreatment to LTFU were large for all outcome measures and treatments ($d > 1.0$), indicating that, across treatment, participants had lower PTSD and drinking scores at LTFU than at pretreatment.

Effect sizes for the post-treatment to LTFU comparison were generally negative, indicating some degree of relapse from post-treatment gains (Table 10). For example, effects sizes for the percentage of days drinking suggested that those who received naltrexone ($d = -.46$) experienced some relapse between post-treatment and LTFU, but not to the extent of those who
received placebo ($d = -1.1$). Both those who did and did not receive PE experienced moderate to high levels of relapse in their percentage of days drinking. Similar results were found for the percentage of heavy drinking days, with an even smaller post-treatment to LTFU effect for naltrexone ($d = -.26$). Finally, participants who received naltrexone continued to demonstrate small improvements in their PTSD symptomatology between post-treatment and LTFU ($d = .26$), relative to those who received placebo ($d = -.07$). Those who received PE had moderate increases in their PTSD symptoms between post-treatment and LTFU ($d = -.58$), while those did not receive PE had small decreases in their PTSD symptoms during this time period ($d = .16$).
Table 10

*Treatment Effect Sizes*

**Medication Effect Sizes**

<table>
<thead>
<tr>
<th>Outcome Measure</th>
<th>N</th>
<th>Pre-FU ES</th>
<th>Post-FU ES</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Days Drinking</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NAL</td>
<td>9</td>
<td>1.42</td>
<td>-0.46</td>
</tr>
<tr>
<td>PBO</td>
<td>9</td>
<td>1.29</td>
<td>-1.1</td>
</tr>
<tr>
<td>% Days Heavy Drinking</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NAL</td>
<td>9</td>
<td>1.36</td>
<td>-0.26</td>
</tr>
<tr>
<td>PBO</td>
<td>9</td>
<td>1.49</td>
<td>-1.47</td>
</tr>
<tr>
<td>PSS-I</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NAL</td>
<td>9</td>
<td>1.66</td>
<td>0.26</td>
</tr>
<tr>
<td>PBO</td>
<td>9</td>
<td>1.23</td>
<td>-0.07</td>
</tr>
</tbody>
</table>

**Prolonged Exposure Effect Sizes**

<table>
<thead>
<tr>
<th>Outcome Measure</th>
<th>N</th>
<th>Pre-FU ES</th>
<th>Post-FU ES</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Days Drinking</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PE</td>
<td>8</td>
<td>1.19</td>
<td>-0.82</td>
</tr>
<tr>
<td>No PE</td>
<td>10</td>
<td>1.22</td>
<td>-0.66</td>
</tr>
<tr>
<td>% Days Heavy Drinking</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PE</td>
<td>8</td>
<td>1.27</td>
<td>-0.73</td>
</tr>
<tr>
<td>No PE</td>
<td>10</td>
<td>1.45</td>
<td>-0.72</td>
</tr>
<tr>
<td>PSS-I</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PE</td>
<td>8</td>
<td>1.24</td>
<td>-0.58</td>
</tr>
<tr>
<td>No PE</td>
<td>10</td>
<td>1.64</td>
<td>0.16</td>
</tr>
</tbody>
</table>

*Note.* ES's in terms of Cohen's d.
Discussion

Posttraumatic stress disorder and alcohol dependence are serious and pervasive disorders that often co-occur, leading to more severe symptomatology and higher levels of general psychopathology (Drapkin, Yusko, Yasinski et al., 2011). These features highlight the need for effective treatments for comorbid PTSD and AD. Recently, researchers have begun to examine effective treatments for this population, and have found that treating both disorders concurrently is effective in addressing both symptom clusters. However, treatment for this population has been inadequately studied in the longer term. Moreover, the long-term effects of CBT on PTSD and naltrexone on AD are not well established and findings are mixed. Therefore, it is important for research to identify treatments that will improve the long-term prospects for patients with comorbid PTSD and alcohol dependence.

An RCT conducted at the University of Pennsylvania and the Philadelphia Veterans Administration between 2001 and 2009 compared the efficacy of an evidence-based treatment for AD (naltrexone), an evidence-based treatment for PTSD (prolonged exposure therapy), their combination, and supportive counseling in patients with comorbid PTSD and AD. Participants in all four treatment groups had large reductions in the percentage of days drinking. However, those who received naltrexone had larger reductions in percent of days drinking than those received placebo. There was also a reduction in PTSD symptoms in all four groups, but no significantly greater reduction among those who received PE compared to those who did not. Six months after treatment, participants in all four groups had increases in the percentage of days drinking. However, those in the combined treatment (PE plus naltrexone) group had the smallest increases. Additionally, exploratory analyses revealed that low PTSD severity levels (≤10 on PSS-I) were achieved at six-month follow-up by 70% of participants who received combination treatment,
55% of participants who received PE only, 44% of participants who received naltrexone only, and 37% of participants in the control group. The study demonstrated that comorbid alcohol dependence and PTSD can be effectively targeted with concurrent efficacious treatments (naltrexone and PE), without exacerbating alcohol use. However, the study is limited in that it followed participants for only six months after treatment discontinuation, precluding any conclusions about the long-term effects of treatment.

The goal of the present study was to conduct a long-term follow-up study (5-10 years after treatment discontinuation) with the aforementioned sample to determine the extent to which treatment gains were maintained during the LTFU period, and whether there were differences in maintenance across treatments. The original study was the first RCT of patients with comorbid alcohol dependence and PTSD to demonstrate significant differences in outcomes between an active treatment and a control comparison. Therefore, the present study represents the first long-term follow-up study of its kind, and one of the few long-term follow-up studies among patients with PTSD and/or AD. Findings from this study provide information on the relative long-term efficacy of treatment for individuals with comorbid PTSD and AD. Additionally, findings help identify barriers to long-term follow-up studies, particularly with this population, which may help increase response rates in future studies.

**Maintenance of Post-Treatment Gains 5-10 Years after Treatment**

The primary research question was whether the treatment gains obtained in the original study regarding PTSD symptoms and drinking behaviors were maintained at long-term follow-up. Previous research on the long-term effects of PE (Resick et al., 2012; Tarrier & Sommerfield, 2004) and naltrexone (Streeton & Whalen, 2001) on PTSD, alcohol dependence, and comorbid populations has yielded mixed results. Findings from the present study revealed that treatment
indeed has long-term efficacy, although there were differences in outcome by treatment group and outcome measure.

**Long-term PTSD outcomes.** The hypothesis that PTSD improvements would maintain at LTFU among those who received PE, but would diminish among those who did not receive PE, was not supported. There were significant reductions in PTSD symptoms between pretreatment and post-treatment for all treatments, and these reductions maintained at LTFU. However, outcomes over time were not based on whether or not participants received PE or naltrexone.

Pre- to post-treatment outcomes among the present sample are similar to those in the original study. The finding that prolonged exposure did not specifically reduce PTSD symptoms is inconsistent with the large body of evidence that PE is an effective treatment for PTSD (e.g., Cahill, Rothbaum, Resick et al., 2009; Foa et al., 2005). Foa and colleagues (2013) explained the null finding of the original study by a) the nonspecific factors involved in supportive counseling received by all groups, and b) relatively low attendance to PE sessions. Long-term follow-up studies of prolonged exposure that originally showed post-treatment differences found that decreases in PTSD symptoms were maintained 5-10 years after treatment (Resick et al., 2012). If Foa and colleagues’ (2013) hypothesis about the contributions of nonspecific therapeutic factors in the original study was valid, the effects of supporting counseling (BRENDA) were sufficiently robust to maintain gains 5-10 years later; however, the strength of this conclusion is mitigated by the fact that there was no control group that did not receive supportive counseling.

Regarding PE attendance, participants in the LTFU completed a mean of 7.5 PE sessions (SD = 4.3) and participants in the original trial completed a mean of 6.2 sessions (SD = 3.9). This is only slightly below the recommended range of 8-15 total PE sessions (Foa, 2011), but
substantially lower than the prescribed dose in the original study (12 weekly sessions followed by 6 biweekly sessions). Additionally, Foa and colleagues (2005) found that, although patients show improvement within the first eight sessions of PE, the majority need additional sessions to reach excellent response. Therefore, it is possible that participants did not receive the optimal dose for treatment effectiveness, which influenced their short-term and long-term PTSD outcomes.

**Long-term drinking outcomes.** The hypothesis that reductions in drinking between pretreatment and post-treatment would be maintained 5-10 years later for those who received naltrexone, but not those who received placebo, was partially supported. Overall, there were significant reductions in percentage of drinking and heavy drinking days between pretreatment and post-treatment. The reductions in percent of days drinking was statistically maintained at LTFU (despite some relapse), but there was significant relapse in the percentage of heavy drinking days between post-treatment and LTFU. Additionally, in general, those who received naltrexone had better outcomes than those who received placebo, but they also were drinking less before treatment began, and naltrexone did not improve drinking outcomes over time.

The present study was the first to examine the effects of naltrexone on alcohol dependence more than one year post-treatment. Previous studies found that the number of drinking days and heavy drinking days is lower in the naltrexone group than placebo group six months to one year post-treatment (Rubio, Manzanares, Lopez-Munoz et al., 2002), but that the advantage diminishes over the follow-up period (O’Malley et al., 1996). Others have found that the effectiveness of naltrexone is no longer statistically significant after a short follow-up period (O’Malley et al., 1996) and that participants benefit more from a long-term course of naltrexone (Rubio et al., 2001). The present findings expand upon these studies, in that the follow-up period
is 5-10 times longer than the aforementioned studies, allowing for a better understanding of the long-term effects of naltrexone after treatment discontinuation. Although there was a main effect of naltrexone (e.g., naltrexone was different from placebo regardless of time point), the non-significant time by naltrexone interaction precludes conclusions about the effect of naltrexone over time. This is potentially due to the small sample size, and effect sizes suggest that there may have been more prominent post-treatment to LTFU differences in drinking behaviors between naltrexone and placebo with a larger sample. A larger follow-up study with significant findings supporting the present effect sizes might mirror others’ evidence of the relative long-term efficacy of naltrexone over placebo (Rubio et al., 2002).

**Long-term outcomes of concurrent treatment.** The hypothesis that post-treatment improvement in PTSD symptoms and drinking behaviors would maintain more among those who received combination treatment than those who received monotherapy (PE alone or naltrexone alone) was partially supported. Among those who received PE only or naltrexone only, treatment type did not influence the trajectory of PTSD symptoms and/or drinking behaviors. However, changes in PTSD symptoms between post-treatment and LTFU varied based on whether or not participants received combination therapy. That is, PTSD symptoms in the combination group continued to slightly improve during this time, while they worsened during this time among participants who received monotherapy. Drinking outcomes, however, did not vary by whether combination treatment was received.

The present findings on the long-term effects of concurrent treatment for comorbid PTSD and alcohol dependence suggest that concurrent treatment is particularly effective in determining the course of PTSD symptoms. Mills and colleagues (2012) found that Concurrent Treatment of PTSD and Substance Use Disorders Using Prolonged Exposure (COPE) plus usual treatment for
substance use disorders, compared with usual treatment alone, resulted in improvements in PTSD symptom severity without an increase in severity of substance dependence. Similarly, Sannibale and colleagues (2013) found that individuals receiving integrated CBT for PTSD and AD had a greater rate of clinically significant change in PTSD severity at post-treatment than individuals receiving CBT for AD only. The present study confirmed and expanded upon these findings through the examination of symptoms 5-10 years after treatment.

Based on the aforementioned studies, it is surprising that PTSD symptoms also continued to improve in the control group. Although not a long-term follow-up study, Hien and colleagues (2009) found no difference in outcome at post-treatment between a cognitive-behavioral treatment for substance use disorders and PTSD and a comparison health education group, despite overall clinically significant reductions in PTSD symptoms. Foa and colleagues (2013) attribute the null finding in Hien and colleagues’ (2009) study to a low rate of treatment completion. This may also explain the present findings, along with the small numbers within each group and the bias involved in those who were located and participated in the LTFU.

It was also surprising that participants in the combination group did not demonstrate superior maintenance in drinking outcomes to those who received PE or naltrexone only. However, Sannibale and colleagues’ (2013) RCT comparing the efficacy of integrated CBT for PTSD and AD to CBT for AD only found that participants in the latter group exhibited larger reductions than those in the integrated treatment group in alcohol consumption, despite the greater rate of clinically significant change in PTSD severity in the integrated treatment group. It may be that focusing on PTSD symptoms detracts from focus on AD. Therefore, it is important to balance the emphasis on PTSD and alcohol dependence symptoms.

**Challenges of LTFU with Present Population**
Participants from the original study were extremely difficult to track and locate for the LTFU study. Among the 120 participants who were pursued from the original study, contact was never established with 86, and 11 had died. Several individuals who were reached requested that the assessment be scheduled at a later date and then did not answer their phone at that time. The final sample for the long-term follow-up study included 19 participants who were assessed 5-10.5 years post-treatment, which represented 12% of the original sample and 22% of the six-month follow-up sample. These results highlight the difficulty in finding participants within the comorbid PTSD and alcohol dependence population 5-10 years after participation in an original trial.

Attrition. Attrition is a problem experienced by many researchers conducting RCTs. Among the 165 randomized participants in the original trial, 53 (32%) participants dropped out of the study prior to the end of the treatment period and 12 (7%) were removed from the study because of serious adverse events. This resulted in a retention rate of 100 (83%) participants at post-treatment. The six-month follow-up sample consisted of 93 (56%) participants from the original randomized sample. These rates are higher than those for other trials of comorbid substance/alcohol dependence and PTSD, which range from 39% to 61% (Brady, Dansky, Back et al., 2001; Kaysen, Schumm, Pedersen et al., 2014; Petrakis, Ralevski, Desai et al., 2012; Sannibale, Teesson, Creamer et al., 2013). They are comparable to retention rates in RCTs for AD, ranging from 64% to 83% (Anton et al., 1999; Anton et al., 2001; Balldin et al., 2003; Laaksonen, Koski-Jannes, Salaspuro et al., 2008; Morris, Hopwood, Whelan, Gardiner, & Drummond, 2001) and PTSD, ranging from 68% to 83% (Foa et al., 1991; Foa et al., 1999; Foa et al., 2005; Resick et al., 2002; Rothbaum et al., 2005). Back and colleagues (2006) found that study completion rates were significantly higher for individuals who demonstrated improvement
in both disorders; therefore, the improvements made by all four groups in the original trial may explain the relatively higher retention rate.

Attrition is particularly problematic in long-term follow-up studies, likely explaining the paucity of long-term follow-up studies (five years post-treatment and beyond) across populations. Several have been conducted for PTSD and other anxiety disorders. Retention rates across LTFU studies for PTSD have included 44% (five years after an RCT; Tarrier & Sommerfield, 2004), 76% (five years after an RCT; Macklin et al., 2000), and 74% (5-10 years after an RCT; Resick et al., 2012). Retention rates in LTFU studies for other anxiety disorders include 30% (8-14 years after an RCT treating generalized anxiety disorder; Durham, Chambers MacDonald et al., 2003), 55% (8-14 years after an RCT; Durham et al., 2003), and 89% (five years after an RCT for social phobia; Hedman, Furmark, Carlbring et al., 2011). Overall, the retention rate in the present study is substantially lower than the aforementioned studies. This is potentially explained by the presence of substance/alcohol abuse or/and comorbid diagnoses, each discussed below.

**Long-term follow-up studies with substance/alcohol dependent populations.** Addiction populations (SUD/AD) are one of the most challenging to study long-term, given their chronic relapsing course and elevated mortality risk (de Bruijn, van den Brink, de Graaf et al., 2006). Among the 120 participants from the original trial that were eligible for participation in the present LTFU, 9% were deceased by LTFU according to public death records. Employment status at baseline predicted mortality, such that the majority in the deceased group were not working or on disability, whereas over one-third in the surviving group were working or in school. These results are consistent with the National Longitudinal Mortality Study (Sorlie & Rogot, 1990). Unemployed men had mortality rates 1.6 and 2.2 times higher than those for
employed Caucasian and African-American men, respectively. Those classified as unable to work had mortality rates from two to seven times the average. In the older age groups (65 and older), low mortality rates were found for those who were still employed. The mortality rates in the present study underscore a major challenge and risk in LTFU studies with addiction populations, and results suggest that assessing and addressing employment status at the beginning of treatment may improve long-term functioning and outcomes.

The low retention rates in long-term follow-up studies with addiction populations are well documented. However, there are differences across the literature in the mechanisms by which these challenges occur. Stout and colleagues (1996) specifically examined factors associated with attrition in a four-year follow-up study of alcohol treatment. The authors identified participant refusal as the primary barrier to long-term retention among individuals with alcohol dependence, contrary to the primary barrier in the present study being unreachable participants.

These differences may reflect the time period and evolution of technology. Landline telephones have become increasingly obsolete between the time of the original study (2001-2009) and LTFU study (2014). An article in the Wall Street Journal (Sparshott, 2013), based on the 2011 Census Bureau data, revealed that more than a quarter of US households have eliminated landline phones and are relying exclusively on cell phones. In 2011, cell phone ownership reached 89%, compared to 36% in 1998. Most participants provided their landline phone number during study participation, and it is possible that they have since transitioned to exclusive use of a cell phone, for which numbers are less accessible to the public. However, even if participants were more easily located, results from Stout and colleagues (1996) suggest that other challenges in LTFU participation may arise.
Long-term follow-up studies in comorbid populations. There is evidence that attrition is particularly high in substance/alcohol dependent populations when there is comorbidity (Beynon, Bellis, & McVeigh, 2006). Given the complicated presentation of psychosocial symptoms in individuals with comorbid PTSD and alcohol dependence, the attrition rate in the present study is not surprising. Previous studies have consistently found vulnerability to poor outcomes, negative consequences, and deleterious effects that intensify over time among patients with comorbid PTSD and SUD/AD (Ouimette, Moos, & Finney, 1998).

These challenges were evident even during the treatment course in Mills and colleagues’ (2012) RCT for individuals with comorbid PTSD and SUD. Among the 103 randomized participants, 16 did not attend any sessions. At six weeks post-baseline, 25 could not be contacted and 4 refused; at three months, 15 could not be contacted and 6 refused; and at 9 months, 18 could not be contacted, 7 refused, and 1 died. This resulted in response rates of 72%, 80%, and 75%, respectively. The authors faced similar challenges in contacting participants as the present study. That Mills et al.’s challenges occurred within a short amount of time, even during study participation, underscores the high risk for attrition in long-term follow up studies with this population. The results of tracking in the present study suggest that that, even with effective treatment for their PTSD and alcohol dependence, participant lives remain chaotic and vulnerable to frequent relocations, homelessness, and death.

The present study found an association between attendance/compliance and participation in long-term follow-up. Almost half of the participants who did not participate in the LTFU study dropped out of treatment before the post-treatment assessment, compared to only one participant out of 19 in the LTFU sample who had stopped attending treatment sessions but completed post-treatment assessments. Additionally, higher attendance to BRENDA (supportive
counseling) sessions and higher levels of medication compliance occurred among individuals who participated in the LTFU study compared to individuals who did not participate (see Table 1). Mills and colleagues (2012) emphasize the importance of future research examining methods to improve retention and compliance in this population, given the severe and chronic symptomatology of the comorbid diagnoses and the other life stressors that make it difficult for them to engage in treatment. Improvements in this area would potentially result in less distress and chaos, and subsequently in the increased availability of long-term follow-up data and improved long-term outcomes.

**Limitations**

Several limitations of the study warrant attention. First, due to the low response rate, the overall sample (and particularly the treatment subsamples) is extremely small. The effect sizes (ES) suggest that the small sample size may have reduced power to detect effects, particularly in planned contrasts of treatment effects between time points. Another limitation is the strong possibility of a biased sample. Tarrier and colleagues (2004) highlight the significant problem subject attrition creates for long-term follow-up studies, such that attrition rates may inflate treatment effects. That is, the individuals who participated were ones whose residence and/or phone plan were stable, either since the original study or in the information found on the internet, suggesting more life stability. This could skew long term outcomes. A third limitation involves the nature of the data collection. The exclusive reliance on self-reports of drinking during follow-up may have resulted in over- or under-reporting of drinking behaviors. Although self-reports of drinking obtained with the Timeline Follow Back interview method have been found to be reliable and valid (Sobell & Sobell, 1992), information from other, corroborating measures, such as liver enzyme levels or collateral reports, would have been useful (O’Malley et al., 1996).
Finally, due to the necessity of balancing comprehensive data with demands on the participant, there are several gaps in the data that preclude an optimal understanding of the long-term post-treatment course and outcomes. Specifically, it is unknown whether participants received other treatments since participation, and whether they are currently on medication for alcohol dependence, PTSD, or other psychiatric conditions. This would be important information, both as a covariate in data analysis and in understanding whether additional treatment further improves long-term outcomes and protects against relapse.

**Implications and Future Directions**

Despite the aforementioned limitations, the present study has several important implications for clinical practice and future research. As previously mentioned, this is the first LTFU study of concurrent treatment for comorbid PTSD and alcohol dependence. The follow-up period is substantially longer than all other AD follow-up studies (which ranged from six months to one year) and most PTSD follow-up studies. The findings demonstrate that the gains obtained in treatment among individuals with comorbid PTSD and AD are maintained to some degree 5 to 10 years later.

Despite some relapse in drinking behaviors, participants maintained significantly lower levels of drinking at LTFU than pretreatment. Although not significant in primary analyses, effect sizes suggest that the relapse rate was higher for those who had received placebo during the study than those who received naltrexone, suggesting positive, long-term effects of naltrexone. Extant literature (Petrakis et al., 2006; Petrakis et al., 2012), coupled with the present study’s results, suggest that naltrexone may be beneficial for long-term outcome in the treatment of comorbid PTSD and AD. However, given the mild to moderate relapse after discontinuation of naltrexone, and evidence suggesting that longer-term treatment with naltrexone is beneficial
(Rubio et al., 2001), future research should continue to determine whether a longer course of treatment might protect even further against relapse, particularly in the areas of heavy drinking.

The post-treatment and LTFU findings provide further evidence against the previously-held notion that trauma-focused therapy is contraindicated for individuals with PTSD and alcohol dependence (Hien, Cohen, Miele et al., 2004; Riggs et al., 2003), and in fact provide support for concurrent treatment in enhancing long-term PTSD outcomes. Overall, the findings of no exacerbated drinking from PE, along with the long-term effectiveness of concurrent treatment on PTSD severity, highlight the safety and efficacy of concurrent treatment in individuals with comorbid PTSD and AD. Therefore, it is not necessary to require extended abstinence prior to beginning PTSD treatment.

More long-term follow-up studies are needed for prolonged exposure, naltrexone, and their combination in treating comorbid PTSD and alcohol dependence. Although the present findings are promising, they are limited by sample size and biases. Therefore, steps should be taken from the outset of treatment to address barriers to long-term follow-up with this population. First, it may be beneficial to maintain contact during the long-term follow-up period, via holiday cards, check-in phone calls, etc. Second, the prospect of intermittent booster sessions should be further explored, as this can potentially reduce the risk of relapse or other burgeoning psychopathology (Gearing, Schwalbe, Lee et al., 2013; Whisman, 1990). Third, given that baseline employment status was associated with mortality between post-treatment and long-term follow-up, as consistent with the National Longitudinal Mortality Study (Sorlie & Rogot, 1990), this is an area that should be addressed in clinical practice by identifying ancillary support services that provide concurrent case management (Mills, Teesson, Back et al., 2012). Prior to beginning treatment, it may be beneficial to motivate unemployed patients to seek employment,
and provide appropriate resources needed for this pursuit. Finally, since treatment completion is a predictor of long-term follow-up participation, techniques should be used to foster treatment adherence and completion. This could involve the use of motivation interviewing, particularly in the beginning of treatment, to build a strong therapeutic alliance through respect and collaboration, assess and address readiness to change, and strengthen motivation and commitment (Miller & Rollnick, 2001).

Conclusion

This study represented the first long-term follow-up to an RCT with patients with comorbid PTSD and alcohol dependence. Findings revealed that participants were generally doing better in PTSD symptomatology and drinking behaviors at long-term follow-up than pretreatment, suggesting that their post-treatment gains had somewhat maintained. The small sample size potentially precluded the detection of significant treatment effects over time. However, there is a clear long-term benefit of concurrent treatment on PTSD symptomatology, and effect sizes suggest that naltrexone may have long-term effects on drinking frequency and intensity. The present study highlighted the vast challenges of conducting a long-term follow-up study with this population. Although several meaningful findings emerged, it is important to address these challenges to obtain a more comprehensive and unbiased understanding of the long-term effects of treatment for all participants.
List of References


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Appendix A

INFORMED CONSENT AND HIPAA AUTHORIZATION FORM/TELEPHONE SCRIPT

Hi (participant name), my name is (caller name) and I'm calling from the Center for the Treatment and Study of Anxiety at the University of Pennsylvania. It is my understanding that you participated in the alcohol study through our clinic in (year). Is that correct?

We’re currently conducting a follow-up study to learn about the long-term effects of treatment. This involves calling all the participants from the alcohol study and asking questions about how you are currently doing with the problems for which you sought treatment years ago. Do you have some time to hear about the study?

The study involves about a one-hour assessment over the telephone asking about your current PTSD symptoms and your drinking behaviors. There is minimal risk of experiencing temporary distress in responding to questions, and you will be contributing to our knowledge about ways to help others maintain sobriety and to recover from trauma. Participation will make you eligible for a lottery for a 50-dollar Target gift card. Winners of the lottery will be randomly selected among the pool of participants. You will be free to stop the evaluation at anytime. Withdrawal will not interfere with your future care.

No further personal health information will be collected beyond that which you provided during your participation in the initial study. The personal health information used in this study includes your name, address, telephone number, and information from the evaluations in the initial study and current study, including psychiatric diagnoses and symptoms, history of traumatic events, and alcohol and drug use. Only the investigator and the study team may use or share your information for the research study. Your information may be held in a research database; however, the School of Medicine may not re-use or re-disclose information collected in this study for a purpose other than this study unless you have given written authorization, the University of Pennsylvania’s Institutional Review Board grants permission, or as permitted by law. Once your personal health information is disclosed to others outside the School of Medicine, it may no longer be covered by federal privacy protection regulations. Your authorization for use of your personal health information for this specific study does not expire.

If you’re interested, I will obtain verbal consent over the phone, and we can either proceed with the assessment at this time or schedule a time that’s more convenient for you. By consenting, you are voluntarily agreeing to take part in the research study. This means that you have been given the pertinent information, your questions have been answered to your satisfaction, and you have decided to volunteer. Would you like to provide verbal consent to participate in the study at this time?

________________________
Name of Patient (Please Print)

________________________
Name of Person Obtaining Consent (Please Print)

________________________
Signature

________________________
Date
Appendix B

PSS-I

Patient Initials ___________                                                        Date ______________
Interviewer_______________________                                      Visit ______________

Ask, "in the past two weeks" (if < 2 weeks since assault, ask "Since the assault"). Probe all positive responses (e.g., "How often has this been happening?")

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<th>1</th>
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<tr>
<td></td>
<td>Not at All</td>
<td>Once per week or less/a little</td>
<td>2 to 4 times per week/somewhat</td>
<td>5 or more times per week/very much</td>
</tr>
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RE-EXPERIENCING (need one): [probe, then quantify]

_____ 1. Have you had recurrent or intrusive distressing thoughts or recollections about the assault?

_____ 2. Have you been having recurrent bad dreams or nightmares about the assault?

_____ 3. Have you had the experience of suddenly reliving the assault, flashbacks of it, acting or feeling as if it were re-occurring?

_____ 4. Have you been intensely EMOTIONALLY upset when reminded of the assault (includes anniversary reactions)?

_____ 5. Have you been having intense PHYSICAL reactions (e.g., sweaty, heart palpitations) when reminded of the assault?

AVOIDANCE (Need three): [probe, then qualify]

_____ 6. Have you persistently been making efforts to avoid thoughts or feelings associated with the assault?

_____ 7. Have you persistently been making efforts to avoid activities, situations, or places that remind you of the assault?

_____ 8. Are there any important aspects about the assault that you still cannot recall?

_____ 9. Have you markedly lost interest in free time activities since the assault?
____10. Have you felt detached or cut off from others around you since the assault?

____11. Have you felt that your ability to experience the whole range of emotions is impaired (e.g., unable to have loving feelings)?

____12. Have you felt that any future plans or hopes have changed because of the assault (e.g., no career, marriage, children, or long life)?

**INCREASED AROUSAL** (need two): [probe then quantify]

____13. Have you had persistent difficulty falling or staying asleep?

____14. Have you been continuously irritable or have outbursts of anger?

____15. Have you had persistent difficulty concentrating?

____16. Are you overly alert (e.g., check to see who is around you, etc.) since the assault?

____17. Have you been jumpier, more easily startled, since the assault?
Appendix C

TLFB Instructions

Now we’re going to work together to come up with the number of times you’ve drank and how much. Do you have a calendar you can use?

Let’s start with yesterday and go back three months. Those dates are (date) to (date). Tell me about personal holidays and events like birthdays, celebrations, hospitalizations, etc to help you recall your activities around those times.

Let’s get started. Have you had any alcohol to drink in the past 3 months?

If NO: Just to be sure, can you think of any times you drank some beer or wine, or hard liquor between (start date) and today?

If YES: We’ve already marked your own personal holidays or special events which we can use to help you call your drinking. Also, people who have fairly regular drinking patterns can use such patterns to help us fill out the calendar.

• When did you last drink during the last three months?
• What was the greatest amount you consumed on any given day in the past 3 months? When did this occur?
• What was the least amount of drinking in the past three months? What did that occur?
• Do you have any patterns to your drinking? Certain days, times, activities?
• During the last three months, did you have any times of abstinence of 7 days or more when you did not drink any alcohol, not even a sip?
  o What was the longest period of total abstinence?
  o What was the next longest period of total abstinence?
• Now, we’ll work our way backward from today and fill in the remaining days for each month
Appendix D

Traumatic Life Events Questionnaire

ID: ___________________________ Date: ___/___/___

I want to know if you’ve experienced any traumatic events since you completed the study. I’m going to go through a list of possible traumas, and tell me if you’ve had any happen to you since the study.

never ___ once ___ twice ___ 3 times ___ 4 times ___ 5 times ___ more than 5 times ___

*If this happened:*
- Did you experience intense fear, helplessness, or horror when it happened? yes/no
- Were you seriously injured? yes/no
- Was someone you cared about or close by seriously injured or killed? yes/no
- Did you think you or a loved one was in danger of being killed by the disaster? yes/no
- How old were you when it first happened? ______

1. Have you experienced a natural disaster (a flood, hurricane, earthquake, etc.)?

2. Were you involved in a motor vehicle accident for which you received medical attention or that badly injured or killed someone?

3. Have you been involved in any other kind of accident where you or someone else was badly hurt? (examples: a plane crash, a drowning or near drowning, an electrical or machinery accident, an explosion, home fire, chemical leak, overexposure to radiation or toxic chemicals)

4. Have you lived, worked or had military service in a war zone? yes/no
   If yes, were you ever exposed to warfare or combat? (for example: in the vicinity of a rocket attack or people being fired upon; seeing someone get wounded or killed)

5. Have you experienced the sudden and unexpected death of a close friend or loved one?

6. Has a loved one ever survived a life threatening or permanently disabling accident, assault, or illness? (examples: spinal cord injury, rape, cancer, serious heart condition, life threatening virus)

7. Have you had a life threatening illness?
   never ___ once ___ twice ___ 3 times ___ 4 times ___ 5 times ___ more than 5 times ___

8. Have you been robbed or been present during a robbery—where the robber(s) used or displayed a weapon?

9. Have you been hit or beaten up and badly hurt by a stranger or by someone you didn’t
know very well?

10. Have you seen a stranger (or someone you didn’t know very well) attack or beat up
someone and seriously injure or kill them?

11. Has anyone threatened or kill you or cause you serious physical harm?

12. Have you been slapped, punched, kicked, beaten up, or otherwise physically hurt by
your spouse (or former spouse), a boyfriend/girlfriend, or some other intimate partner?

13. Did anyone touch sexual parts of your body or make you touch sexual parts of their
body—against your will or without your consent?

14. Has anyone stalked you—in other words: followed you or kept track of your activities—
causing you to feel intimidated or concerned for your safety?

15. Have you or a romantic partner had a miscarriage?

16. Have you or a romantic partner had an abortion?

17. Have you experienced (or seen) any other events that were life threatening, caused serious
injury, or were highly disturbing or distressing? (examples: lost in the wilderness; a serious
animal bite; violent death of a pet; being kidnapped or held hostage; seeing a mutilated body
or body parts)
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